Appendix 1: medical history report of enrolled patients

Case 1

The first patient did not present relevant pre-existing comorbidities. On day 0, patient 1 reached the emergency department of our hospital for fever and dyspnea, presenting a positive swab-test for COVID-19. Due to a rapid worsening of clinical condition, the patient was admitted to ICU on day 2. In ICU, a pharmacological therapy with steroids and low molecular weight heparin (LMWH) was started, supporting respiratory activity through high-flow nasal canula (HFNC) in prone position during night hours. In order to tolerate NIV, a sedation with remifentanil at low dosage was performed during night hours. On day 9, in place of remifentanil, we started sedation with remimazolam according to defined protocol criteria, with an infusion rate of 0.05 mg/kg/h. The drug's administration was stopped after 7 hours 55 minutes, without modifications of the initial dosage. No adverse events were registered during remimazolam infusion.

Case 2

Patient 2 presented a positive Covid swab test in January 2021. Despite home-therapy with steroids, antibiotics and LMWH, clinical conditions worsened until to hospital admission and following ICU recovery 8 days later (day 0). In order to improve respiratory function, HFNC was adopted during night hours with the association of remifentanil infusion. On day 12, at 10.35 pm, we started the infusion of remimazolam, instead of remifentanil, according to defined protocol. The infusion rate was of 0.05 mg/kg/h for the following 7 hours 25 minutes, until 6 am. No adverse events were registered during infusion of remimazolam.

Case 3

On day 0, patient 3 was admitted to emergency department for loss of consciousness, fever, and seizures. The swab for COVID was positive. Due to a continuous worsening of respiratory function, the patient was admitted to ICU on day 7. During ICU stay, patient was managed with HFNC, mini tracheotomy for secretions, norepinephrine administration, continuous renal replacement therapy (CRRT). The patient presented important neurological alterations with the need of sedative drugs administration (dexmedetomidine, remifentanil, gabapentin, chlorpromazine).

Remimazolam was administered according to protocol criteria on days 23 and 24 during night hours (11 pm to 6 am, during both days, total infusion time 15 h, with an infusion rate of 0.09 mg/kg/h). No adverse events were registered during remimazolam infusion.

Case 4

Patient 4 was admitted to the emergency department of our hospital for dyspnea (day 0). Due to a rapid worsening of respiratory conditions, NIV was adopted [continuous positive airway pressure (CPAP)]. COVID swab was positive; furthermore, computer tomography (CT) showed signs of pneumonia and an echocardiographic evaluation diagnosed an important reduction in the ejection fraction (20%) with complete hypokinesia. On the same day, the patient was intubated and admitted to ICU, to receive mechanical ventilation. To manage hypotension and hemodynamic instability, continuous administrations of epinephrine and norepinephrine were adopted. Sedation was achieved with propofol and remifentanil administration.

Remimazolam infusion was started at 11.25 pm on day 12, with a starting dose of 0.05 mg/kg/h. The dosage was titrated between 0.05 and 2 mg/kg/h according to CONOX values. After 8 hours, observing an adequate hemodynamic stability, the dosage of norepinephrine was reduced (from 0.25 mcg/kg/min to 0.1 mcg/kg/min). Remimazoalm administration was interrupted after 61 hours without relevant side effects.

https://dx.doi.org/10.21037/jeccm-24-123

Case 5

The fifth patient presented a positive COVID swab during December 2021, with the need for ICU admission on day 9 after worsening of clinical condition. In order to support respiratory function, patient started HFNC alternated to CPAP, both NIV were stopped for clinical inefficacy and pneumomediastinum. On day 39 the patient was intubated and mechanically ventilated. Sedation was obtained with continuous infusion of propofol, midazolam and remifentanil. Hemodynamic instability required the start of norepinephrine at high dosage. Remimazolam perfusion started at 11.35 pm on day 42 until 8:00 am of the day after. Propofol and midazolam were stopped during remimazolam infusion; the dosage was titrated between 0.05 and 0.4 mg/kg/h according to CONOX values. The patient died on day 45 for multi-organ failure and severe hypoxic respiratory collapse.

https://dx.doi.org/10.21037/jeccm-24-123

Table S1 Arterial blood gas analyses for each patient at different time-point intervals

Parameters	Patient 1			Patient 2			Patient 3			Patient 4			Patient 5		
	Basal	1 h	8 h	Basal	1 h	8 h	Basal	1 h	8 h	Basal	1 h	8 h	Basal	1 h	8 h
pH	7.51	7.48	7.48	7.38	7.43	7.37	7.42	7.44	7.42	7.46	7.44	7.46	7.34	7.36	7.36
PaO_2 (mmHg)	84	77	87.3	96.4	105.5	130	114	84.4	89	80.2	76.6	70.1	94.2	87.1	88.7
$PaCO_2$ (mmHg)	37	35.7	40.5	43.7	39.9	55.5	39	37.7	41.3	65.7	70.1	68.6	58.9	62.3	64
HCO_3^- (mmol/L)	29.8	27	30	25.8	26	32.1	25	24.9	26.6	42.3	45	45	31.3	34.6	35.6
Lactate (mmol/L)	1.35	1.40	1.45	0.55	0.6	0.54	1.39	1.16	1.30	1.96	2.12	2.39	1.92	1.94	2.21
FiO_2	0.65	0.65	0.65	0.6	0.6	0.6	0.6	0.6	0.6	0.7	0.7	0.7	0.9	0.9	0.9

FiO_2, fraction of inspired oxygen; HCO_3^-, blood bicarbonate; PaO_2, arterial partial oxygen tension; $PaCO_2$, arterial partial carbon dioxide tension.

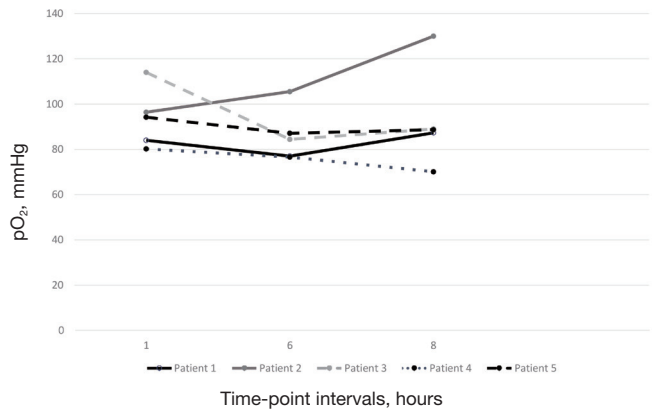

Figure S1 pO_2 values for each patient at different time-point intervals (at 1, 6, and 8 hours after starting remimazolam infusion).

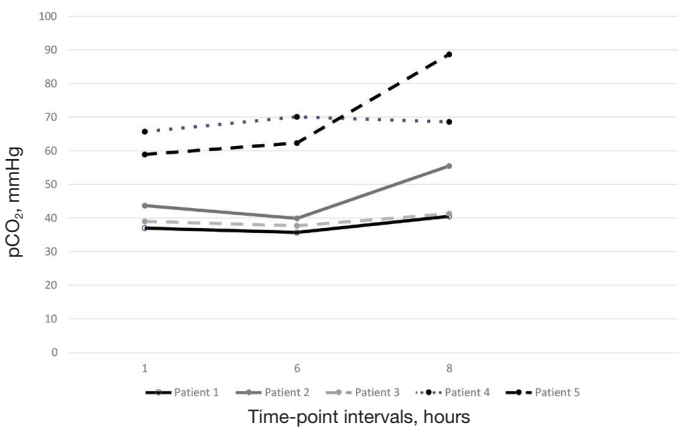

Figure S2 pCO_2 values for each patient at different time-point intervals (at 1, 6, and 8 hours after starting remimazolam infusion).

https://dx.doi.org/10.21037/jeccm-24-123

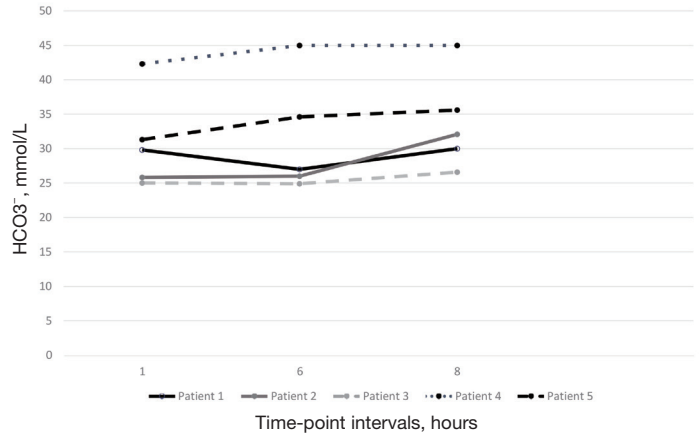

Figure S3 $HCO3^-$ values for each patient at different time-point intervals (at 1, 6, and 8 hours after starting remimazolam infusion).

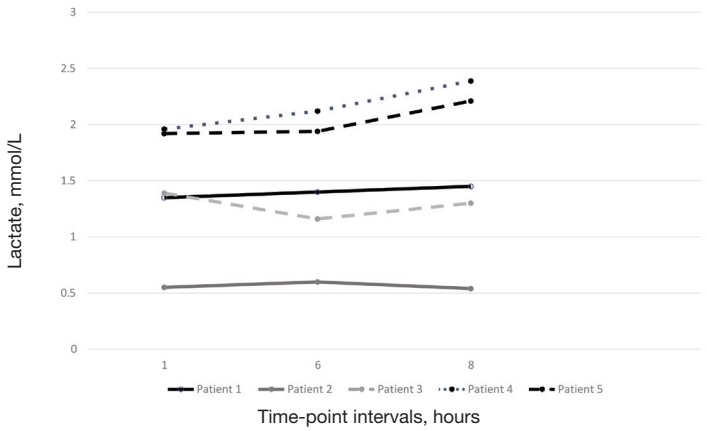

Figure S4 Lactate values for each patient at different time-point intervals (at 1, 6, and 8 hours after starting remimazolam infusion).

https://dx.doi.org/10.21037/jeccm-24-123

Table S2 Hemodynamic parameters measured at different time-point intervals

Patient	Basal				1 h				6–8 h			
	HR (bpm)	SAP (mmHg)	DAP (mmHg)	MAP (mmHg)	HR (bpm)	SAP (mmHg)	DAP (mmHg)	MAP (mmHg)	HR (bpm)	SAP (mmHg)	DAP (mmHg)	MAP (mmHg)
1	75	110	65	81	73	104	59	75	70	103	60	76
2	91	154	63	96	96	124†	83†	102	75	135	50†	85
3	49	107	49	69	49	100	48	65	45	125†	55	78
4	97	110	56	72	94	130	65	94†	108	112	65	59†
5	116	94	51	65	105	119†	57	77	109	126	57	78

A substantial hemodynamic stability was observed in all patients. †, >20% variation compared to previous measurement. DAP, diastolic arterial pressure; HR, heart rate; MAP, mean arterial pressure; SAP, systolic arterial pressure.

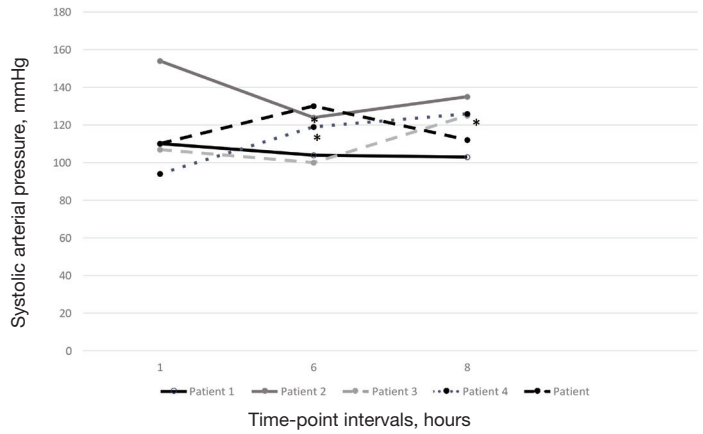

Figure S5 Systolic arterial pressure values for each patient at different time-point intervals (at 1, 6, and 8 hours after starting remimazolam infusion). *, >20% variation compared to previous measurement.

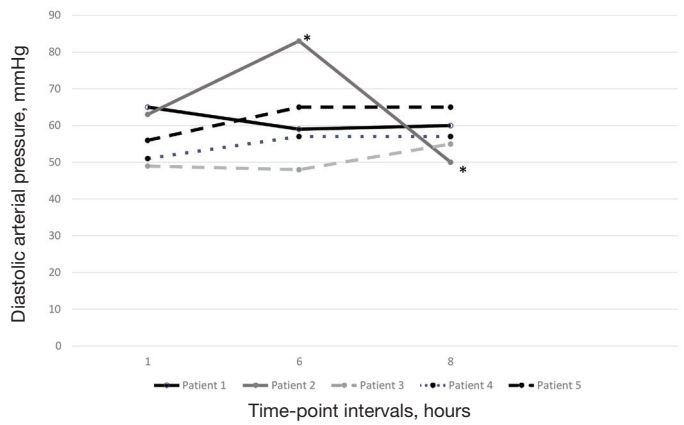

Figure S6 Diastolic arterial pressure values for each patient at different time-point intervals (at 1, 6, and 8 hours after starting remimazolam infusion). *, >20% variation compared to previous measurement.

https://dx.doi.org/10.21037/jeccm-24-123