

بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

بررسی وضعیت بالینی 195 بیمار مبتلا به کووید 19 در چند مرکز  
مطالعه از نوع گذشته نگر

استاد راهنما : جناب آقای دکتر براهیمی

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**ABSTRACT—Introduction:**Coronavirus disease-2019 (COVID-19) outbreak has spread around the world. However, the dynamic course of critically ill COVID-19 has not been described thoroughly.**Patients and Methods:**We retrospectively analyzed 195 critically ill COVID-19 patients in Hubei province, China, between January 5, 2020 and April 3, 2020. Epidemiologic data, clinical features, treatments, and outcomes were collected and analyzed.**Results:**Most critically ill patients were older with higher Acute Physiology and Chronic Health Evaluation II scores. After critical illness onset, a total of 181 (92.8%) patients received ventilation support, of which 84 (43.1%) received noninvasive and 97 (49.7%) received invasive mechanical ventilation (IMV). Among the 97 patients with IMV, 28 (28.9%) received prone ventilation, 57 (58.8%)

The overall mortality of critically ill patients at day 28 was 42.1%. Intensive care unit (ICU) mortality was around 33%, as 16 patients died prior to ICU admission. A low PaO<sub>2</sub>/FiO<sub>2</sub> ratio was an independent risk factor for death. High viral load was observed in most non-survivors. Conclusion: ARDS and shock were notable in the critical illness of COVID-19. Ventilation support and hemodynamic support were the cornerstones for critical care. High viral load was associated with death of critically ill COVID-19 patients.

**KEYWORDS**—Coronavirus, critical illness, infection

**ABBREVIATIONS**—AKI—acute kidney injury; APACHE II—Acute Physiology and Chronic Health Evaluation II; ARDS—

acute respiratory distress syndrome; BMI—body mass index; COVID-19—Corona Virus Disease-2019; CRRT—continuous

# INTRODUCTION

- AT THE END OF 2019, A NOVEL CORONAVIRUS WAS IDENTIFIED AS THE CAUSE OF A CLUSTER OF PNEUMONIA IN WUHAN, CHINA (1).
- IN FEBRUARY 2020, THE PNEUMONIA WAS NAMED CORONAVIRUS DISEASE-2019 (COVID-19), AND THE VIRUS THAT CAUSED COVID-19 WAS DESIGNATED AS SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS 2 (SARS-COV-2) (2).

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- A SINGLE-CENTERED, RETROSPECTIVE, STUDY INCLUDED 52 CRITICALLY ILL PATIENTS WHO WERE ADMITTED TO THE ICU OF WUHAN JIN YIN-TAN HOSPITAL (WUHAN, CHINA) AND REPORTED THAT THE 28-DAY MORTALITY OF CRITICAL ILLNESS WAS UP TO 61.5% (5).
- HOWEVER, THE CLINICAL COURSE OF CRITICALLY ILL PATIENTS WITH COVID-19 DURING HOSPITALIZATION WAS NOT ENTIRELY DESCRIBED.

- THE IN-DEPTH UNDERSTANDING OF COVID-19-RELATED CRITICAL ILLNESS IS USEFUL FOR EARLY IDENTIFICATION AND TRIAGING PATIENTS AT RISK OF DEATH; RATIONAL ALLOCATION OF THE HEALTH CARE RESOURCES AND BETTER MANAGEMENT OF THE CRITICAL ILLNESS; SHARING THE THERAPEUTIC EXPERIENCE AND PROVIDING BASELINE COVID-19-ASSOCIATED COMPLICATION AND MORTALITY DATA.
- HEREIN, WE ANALYZED THE CLINICAL COURSE OF 195 CRITICALLY ILL COVID-19 PATIENTS DURING HOSPITALIZATION



# PATIENTS AND METHODS

- STUDY DESIGN AND PARTICIPANTS WE RETROSPECTIVELY STUDIED ALL CRITICALLY ILL PATIENTS WITH COVID-19 ADMITTED TO ZHONGNAN HOSPITAL OF WUHAN UNIVERSITY, LEISHENSHAN HOSPITAL, HUANGGANG CENTRAL HOSPITAL, AND XISHUI PEOPLE'S HOSPITAL BETWEEN JANUARY 5, 2020 AND

- EPIDEMIC AND DEMOGRAPHIC DATA BETWEEN JANUARY 5, 2020 AND APRIL 3, 2020, 3,749 PATIENTS WITH COVID-19 WERE ADMITTED TO THE FOUR MEDICAL CENTERS; 195 CRITICALLY ILL PATIENTS (3.0%) WERE INCLUDED AND 82 CRITICALLY ILL PATIENTS (42.1%) DIED AT 28 DAYS AFTER THE ONSET OF CRITICAL ILLNESS (FIG. 1). OF ALL 195 CRITICALLY ILL PATIENTS, THE MEDIAN AGE WAS 66.0 (IQR, 56.0–76.0) YEARS; 130 (66.7%) WERE MALE (TABLE 1). COMORBIDITIES WERE COMMON IN 137 PATIENTS (70.3%).

- APRIL 3, 2020. ALL PATIENTS WERE CONSECUTIVE. COVID-19 WAS DIAGNOSED ACCORDING TO THE WORLD HEALTH ORGANIZATION'S INTERIM GUIDANCE (7).
- CRITICALLY ILL PATIENTS WERE DEFINED AS THOSE ADMITTED TO THE ADULT ICU OR THOSE REQUIRING MECHANICAL VENTILATION (INVASIVE OR NONINVASIVE), THOSE WITH A FRACTION OF INSPIRED OXYGEN (FIO<sub>2</sub>) CONCENTRATION GREATER THAN OR EQUAL TO 60%, OR THOSE WITH THE NEED FOR INTRAVENOUS INFUSION OF VASOPRESSORS (8, 9).

- ZHONGNAN HOSPITAL OF WUHAN UNIVERSITY AND LEISHENSHAN HOSPITAL ARE LOCATED IN WUHAN, THE CENTER OF COVID-19 OUTBREAK.
- HUANGGANG CENTRAL HOSPITAL AND XISHUI PEOPLE'S HOSPITAL ARE LOCATED IN HUANGGANG, 100 KM TO THE EAST OF WUHAN.
- THE FOUR MEDICAL CENTERS WERE ASSIGNED TO ACCEPT AND TREAT THE COVID-19 PATIENTS BY THE GOVERNMENT DURING THE DISEASE OUTBREAK.
- THIS CASE SERIES WAS APPROVED BY THE INSTITUTIONAL ETHICS BOARD OF THE FOUR MEDICAL CENTERS.
- ORAL CONSENT WAS OBTAINED FROM PATIENTS. THE TIME FRAME OVERLAPS WITH THAT OF A PREVIOUSLY REPORTED CASE SERIES, AND 33 PATIENTS IN THE CURRENT REPORT HAVE BEEN INCLUDED IN THE PREVIOUS CASE SERIES (3).

- REAL-TIME REVERSE TRANSCRIPTION POLYMERASE CHAIN REACTION ASSAY FOR SARS-COV-2  
THE METHODOLOGY OF REAL-TIME QUANTITATIVE PCR (RT-PCR) HAS BEEN PREVIOUSLY  
REPORTED (3).
- THROAT SWAB SAMPLES WERE COLLECTED AND PLACED INTO A COLLECTION TUBE WITH  
1.50ML OF VIRUS PRESERVATION SOLUTION, AND TOTAL RNA WAS EXTRACTED WITHIN 2 H  
USING THE RESPIRATORY SAMPLE RNA ISOLATION KIT (ZHONGZHI, WUHAN, CHINA).
- IN BRIEF, 40ML OF CELL LYSATES WERE TRANSFERRED INTO A COLLECTION TUBE FOLLOWED BY  
VORTEX FOR 10 S.

- AFTER STANDING AT ROOM TEMPERATURE FOR 10 MIN, THE COLLECTION TUBE WAS CENTRIFUGED AT 1,000 RPM/MIN FOR 5 MIN.
- THE SUSPENSION WAS USED FOR REAL-TIME REVERSE TRANSCRIPTION POLYMERASE CHAIN REACTION (RT-PCR) ASSAY OF SARS-COV-2.
- TWO TARGET GENES, INCLUDING OPEN READING FRAME1A (ORF1AB) AND NUCLEOCAPSID PROTEIN (N), WERE SIMULTANEOUSLY AMPLIFIED AND TESTED DURING THE REAL-TIME RT-PCR ASSAY

- TARGET 1 (ORF1AB):
- REAL-TIME RT-PCR ASSAY WAS PERFORMED USING A SARS-COV-2 NUCLEIC ACID
- DETECTION KIT ACCORDING TO THE MANUFACTURER'S PROTOCOL (SHANGHAI BIO-GERM
- MEDICAL TECHNOLOGY CO LTD). THE REACTION MIXTURE CONTAINS 12ML OF REACTION
- BUFFER, 4ML OF ENZYME SOLUTION, 4ML OF PROBE PRIMERS SOLUTION, 3ML OF
- DIETHYL PYROCARBONATE-TREATED WATER, AND 2ML OF RNA TEMPLATE. THE RT-PCR

- ASSAY WAS PERFORMED UNDER THE FOLLOWING CONDITIONS: INCUBATION AT 50°C FOR 15 MIN AND 95°C FOR 5 MIN, 40 CYCLES OF DENATURATION AT 94°C FOR 15 S AND EXTENDING AND COLLECTING FLUORESCENCE SIGNAL AT 55°C FOR 45 S. A CYCLE THRESHOLD VALUE (CT-VALUE) LESS THAN 37 WAS DEFINED AS A POSITIVE TEST RESULT, AND A CT-VALUE OF 40 OR MORE WAS DEFINED AS A NEGATIVE TEST.
- A MEDIUM LOAD, DEFINED AS A CT-VALUE OF 37 TO LESS THAN 40, REQUIRED CONFIRMATION BY RETESTING



# DATA COLLECTION

- THE DATA WERE EXTRACTED FROM THE MEDICAL RECORDS OF PATIENTS. THE RESEARCH TEAM OF THE DEPARTMENT OF CRITICAL CARE MEDICINE AT ZHONGNAN HOSPITAL OF WUHAN UNIVERSITY ANALYZED AND REVIEWED THE DATA.
- DATA COLLECTION INCLUDED EPIDEMIC DATA, DEMOGRAPHIC DATA, COMORBIDITIES, SYMPTOMS AND SIGNS, LABORATORY FINDINGS, RADIOLOGIC FINDINGS, RESPIRATORY MECHANICS VARIABLES, COMPLICATIONS, TREATMENTS, AND TIME COURSE OF THE ILLNESS.
- THE SEVERITY OF THE ILLNESS WAS ASSESSED USING THE ACUTE PHYSIOLOGY AND CHRONIC HEALTH EVALUATION II (APACHE II) SCORE, AND ORGAN DYSFUNCTION WAS ASSESSED USING THE SEQUENTIAL ORGAN FAILURE ASSESSMENT (SOFA) SCORE. VENTILATORY PARAMETERS, ARTERIAL BLOOD GAS VALUES, LABORATORY VALUES, AND SOFA SCORES WERE FOLLOWED ON 1, 3, 7, 14, AND 21 DAYS AFTER CRITICAL ILLNESS ONSET

- . LIVING STATUS AT 28 DAYS AFTER THE ONSET OF CRITICAL ILLNESS WAS RECORDED. ARDS WAS DIAGNOSED ACCORDING TO THE BERLIN DEFINITION AND ACUTE KIDNEY INJURY (AKI) WAS DIAGNOSED ACCORDING TO THE KIDNEY DISEASE: IMPROVING GLOBAL OUTCOMES CLINICAL PRACTICE GUIDELINES (10, 11).
- SHOCK WAS DEFINED ACCORDING TO THE DEFINITION OF SEPSIS 3.0 (12). ACUTE CARDIAC INJURY WAS DEFINED AS BLOOD LEVELS OF HYPERSENSITIVE TROPONIN I ABOVE THE UPPER REFERENCE LIMIT (>26.2 PG/ML).
- THE TIME TO SARS-COV-2 RNA CLEARANCE IN RESPIRATORY SECRETIONS BY RT-PCR WAS DEFINED AS THE TIME FROM ILLNESS ONSET UNTIL THE TEST WAS NEGATIVE ON TWO OCCASIONS, WITHOUT A POSITIVE TEST AFTERWARD

# STATISTICAL ANALYSIS

- KAPLAN–MEIER METHOD WAS USED TO DEPICT THE PROBABILITY OF SURVIVAL OVER THE DURATION OF FOLLOW-UP AND TO GENERATE SURVIVAL CURVES.
- UNIVARIATE ANALYSES WERE PERFORMED TO EVALUATE THE RISK FACTORS ASSOCIATED WITH DEATH. MULTIVARIABLE LOGISTIC REGRESSION ANALYSIS WAS USED TO IDENTIFY INDEPENDENT PREDICTORS OF MORTALITY.
- FOR ALL STATISTICAL TESTS, A TWO-SIDED  $\alpha$  OF LESS THAN 0.05 WAS CONSIDERED STATISTICALLY SIGNIFICANT.
- SPSS (STATISTICAL PACKAGE FOR THE SOCIAL SCIENCES) VERSION 24 SOFTWARE (SPSS INC) WAS USED FOR ALL ANALYSES

- CATEGORICAL VARIABLES WERE SHOWN AS FREQUENCY RATES AND PERCENTAGES, WHILE CONTINUOUS VARIABLES WERE DESCRIBED USING MEAN AND STANDARD DEVIATIONS OR MEDIANS AND INTERQUARTILE RANGE (IQR) VALUES.
- INDEPENDENT GROUP TESTS OR THE MANN–WHITNEY TEST WAS USED FOR CONTINUOUS VARIABLES AS APPROPRIATE.
- PROPORTIONS FOR CATEGORICAL VARIABLES WERE COMPARED USING THE CHI-SQUARE TEST, ALTHOUGH THE FISHER EXACT TEST WAS USED WHEN THE DATA WERE LIMITED. THE

- RESULTS EPIDEMIC AND DEMOGRAPHIC DATA BETWEEN JANUARY 5, 2020 AND APRIL 3, 2020, 3,749 PATIENTS WITH COVID-19 WERE ADMITTED TO THE FOUR MEDICAL CENTERS; 195 CRITICALLY ILL PATIENTS (3.0%) WERE INCLUDED AND 82 CRITICALLY ILL PATIENTS (42.1%) DIED AT 28 DAYS AFTER THE ONSET OF CRITICAL ILLNESS (FIG. 1). OF ALL 195 CRITICALLY ILL PATIENTS, THE MEDIAN AGE WAS 66.0 (IQR, 56.0–76.0) YEARS; 130 (66.7%) WERE MALE (TABLE 1). COMORBIDITIES WERE COMMON IN 137 PATIENTS (70.3%).
- THE MOST COMMON COMORBIDITIES WERE HYPERTENSION (45.6%) AND DIABETES (28.2%).

- ORGAN DYSFUNCTION ON DAY 1 ON DAY 1 AFTER CRITICAL ILLNESS ONSET, THE MEDIAN APACHE II SCORE AND SOFA SCORE WERE 14.0 (IQR, 11.0–17.0) AND 6.0 (IQR, 4.0–9.0), RESPECTIVELY (TABLES 1 AND 2).
- ARTERIAL BLOOD GAS ANALYSIS REVEALED THE MEDIAN PH VALUE AS 7.42 (IQR, 7.38–7.48) WITH A PACO<sub>2</sub> OF 36.8 (IQR, 31.8–40.95) MM HG.
- THE MEDIAN PAO<sub>2</sub>/FIO<sub>2</sub> RATIO AND LACTATE LEVEL WERE 101 (IQR, 73–151) MM HG AND 1.8 (IQR, 1.3–2.5) MMOL/L, RESPECTIVELY. INCREASED NEUTROPHIL COUNT AND LYMPHOPENIA WERE REPORTED.
- ADDITIONALLY, PROLONGED PROTHROMBIN TIME AND INCREASED ASPARTATE AMINOTRANSFERASE LEVELS WERE OBSERVED. MEDIAN ASPARTATE AMINOTRANSFERASE WAS 43 (IQR, 28–69) U/L

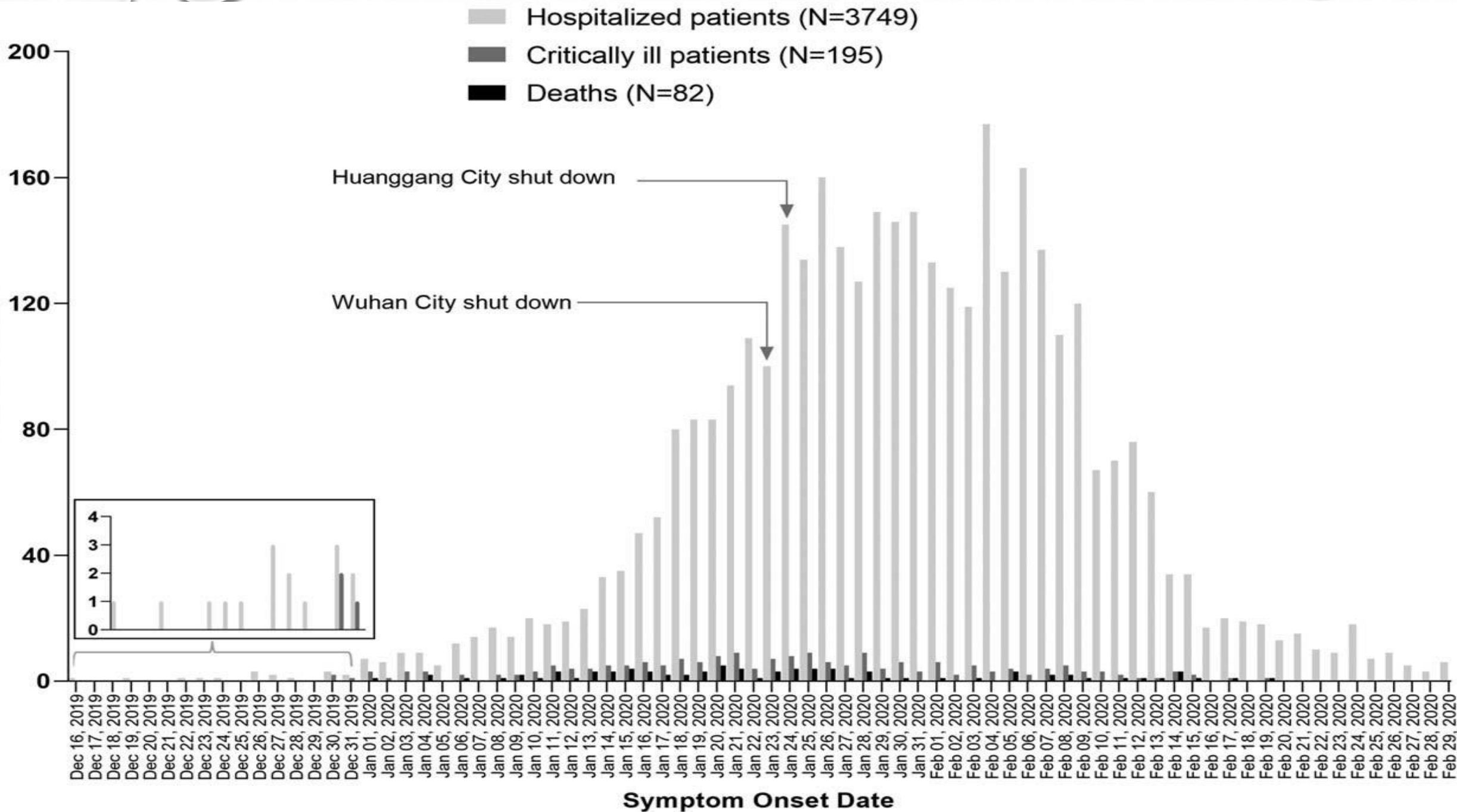
- ORGAN DYSFUNCTION FROM WEEK 1 TO WEEK 3 ORGAN DYSFUNCTION FROM WEEK 1 TO WEEK 3 IS SHOWN IN TABLE 2 AND FIGURE 2. FOR THE SURVIVORS, THE  $PAO_2$  AND  $PAO_2/FIO_2$  RATIOS BEGAN TO IMPROVE DURING WEEK 2. FOR THE NON-SURVIVORS,  $PACO_2$  GRADUALLY INCREASED AND SEVERE HYPOXEMIA WAS PERSISTENT FROM WEEK 1 TO WEEK 3. DURING WEEK 3, NOTABLE HIGH  $PACO_2$  LEVELS WERE SHOWN IN NON-SURVIVORS.

- FOR PATIENTS WHO RECEIVED MECHANICAL VENTILATION, TIDAL VOLUME WAS SET AS 5 ML TO 7 ML PER KG OF PREDICTED BODY WEIGHT, PLATEAU PRESSURE RANGED FROM 20 CMH<sub>2</sub>O TO 25 CMH<sub>2</sub>O AND POSITIVE END-EXPIRATORY PRESSURE (PEEP) WAS 8 CMH<sub>2</sub>O TO 10 CMH<sub>2</sub>O.
- FOR THE PATIENTS WITH VENTILATOR DEPENDENCE, THE SET PEEP LEVEL WAS DOWN TO 5 (IQR, 5.0–6.0) CMH<sub>2</sub>O DUE TO THE IMPROVED PULMONARY EDEMA ASSOCIATED WITH ARDS IN WEEK 3.



- WEEK 3. THE PATIENTS WITH VENTILATOR DEPENDENCE AFTER WEEK 3 SHOWED A RETICULAR PATTERN OF LUNG INFILTRATION, AND REPRESENTATIVE IMAGES OF CT SCAN ARE SHOWN IN FIGURE 3.
- OVER THE COURSE OF CRITICAL ILLNESS, 89 PATIENTS PRESENTED WITH HYPOTENSION REQUIRING VASOPRESSORS. ETIOLOGIES OF SHOCK INCLUDED SEPTIC SHOCK (78 CASES), HYPOVOLEMIC SHOCK (SEVEN CASES), CARDIOGENIC SHOCK (SIX CASES), AND UNKNOWN CAUSES (THREE CASES).

No. of Patients



Over the course of critical illness, 89 patients presented with hypotension requiring vasopressors. Etiologies of shock included septic shock (78 cases), hypovolemic shock (seven cases), cardiogenic shock (six cases), and unknown causes (three cases). Among the 89 patients, four presented with

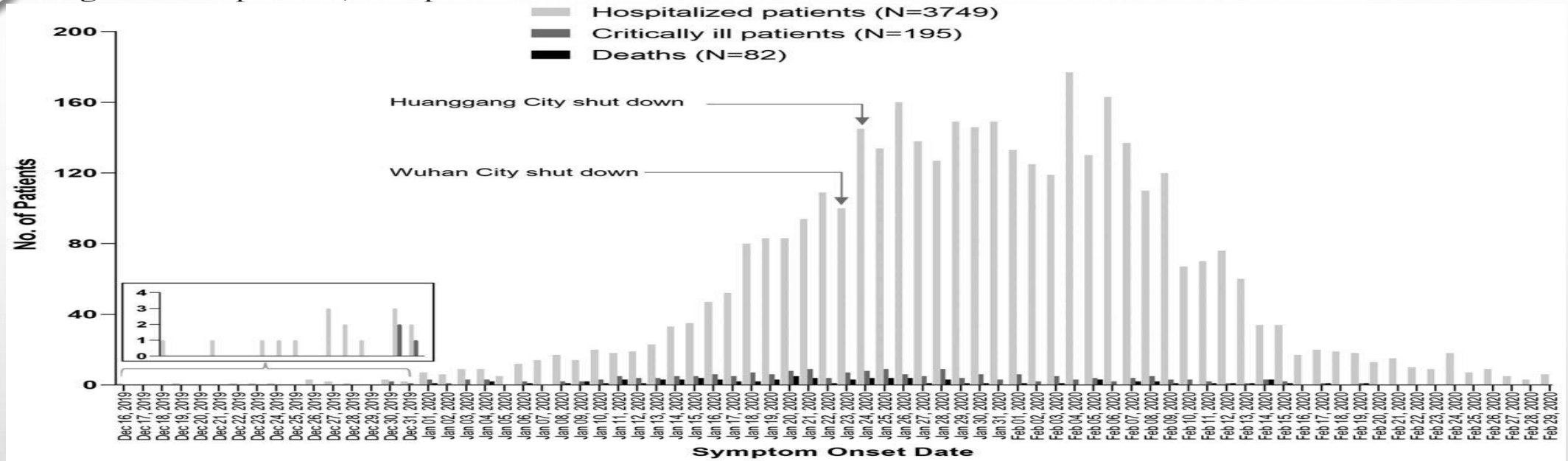


FIG. 1. Hospitalized patients, critically ill patients and deaths with COVID in four medical centers located in Wuhan City and Huanggang City between December 30, 2019 and February 19, 2020. Four medical centers included Zhongnan Hospital, Wuhan University; Leishenshan Hospital, Wuhan; Huanggang Central Hospital, Huanggang; and Xishui People's Hospital, Huanggang. COVID indicates coronavirus disease.

TABLE 1. Baseline characteristics and laboratory data in 195 critically ill patients with COVID-19

	Normal range	Total (n % 195)
Age, years	NA	66.0 (56.0–76.0)
Sex	NA	
Male	NA	130 (66.7)
Female	NA	65 (33.3)
Any comorbidity	NA	137 (70.3)
APACHE II score	NA	14.0 (11.0–17.0)
Arterial blood gas		
PH	7.35–7.45	7.42 (7.38–7.48)
PaO <sub>2</sub> , mm Hg	83–108	64.10 (48.75–74.00)
PaO <sub>2</sub> /FiO <sub>2</sub>	400–500	101 (73–151)
PaCO <sub>2</sub> , mm Hg	35–48	36.80 (31.80–40.95)
Bicarbonate, mmol/L	22–27	23.40 (21.55–25.50)
Lactate, mmol/L	0.5–1.6	1.80 (1.30–2.50)
White blood cell count, 10 <sup>9</sup> /L	3.5–9.5	8.89 (5.94–12.74)
Neutrophil count, 10 <sup>9</sup> /L	1.8–6.3	7.50 (5.05–11.16)
Lymphocyte count, 10 <sup>9</sup> /L	1.1–3.2	0.61 (0.39–0.86)
Platelet count, 10 <sup>9</sup> /L	125–350	161 (114–208)
Prothrombin time, s	9.4–12.5	13.0 (11.9–14.5)
Hypersensitive troponin I, >26.2 pg/mL	0–26.2	61 (31.3)

•COMPLICATION AND NOSOCOMIAL INFECTION

- OVER THE COURSE OF DAYS 1 TO 28, 184 (94.4%) PATIENTS PRESENTED LYMPHOPENIA, 162 (83.1%) PRESENTED WITH ARDS, AND 89 (45.6%) PRESENTED WITH SHOCK. ACUTE KIDNEY INHYPERTENSION WAS IDENTIFIED IN 10 CASES AND REPRESENTATIVE ECHOCARDIOGRAM WAS SHOWN IN MOVIE 1 (SUPPLEMENTAL DIGITAL CONTENT 1, VIDEO 1, [HTTP://LINKS.LWW.COM/SHK/B111](http://links.lww.com/shk/B111)). LESS COMMON COMPLICATIONS WERE CEREBRAL INFARCTION (SIX CASES, 3.1%), DEEP VEIN THROMBOSIS (FOUR CASES, 2%), CEREBRAL HEMORRHAGE (TWO CASES, 1%), MYOCARDIAL INFARCTION (TWO CASES, 1.0%), AND SUSPECTED PULMONARY EMBOLISM (ONE CASE, 0.5%).JURY OCCURRED IN 58 CASES (29.7%). ARDS-INDUCED PULMONARY

	Normal range	Day 1 (n ¼ 195)	Day 3 (n ¼ 178)	Day 7 (n ¼ 159)	Day 14 (n ¼ 124)	Day 21 (n ¼ 98)
SOFA	NA	6.0 (4.0–9.0)	4.0 (3.0–6.0)	4.0 (3.0–7.2)	4.0 (2.0–7.0)	4.0 (1.3–8.5)
PaO <sub>2</sub> , mm Hg	83–108	64.10 (48.75–74.00)	64.20 (53.30–78.50)	68.00 (57.00–84.00)	71.40 (59.70–85.15)	80.80 (63.90–92.10)
PaCO <sub>2</sub> , mm Hg	35–48	36.80 (31.80–40.95)	39.50 (34.40–45.30)	40.75 (35.00–48.80)	46.00 (39.00–51.80)	49.00 (34.80–57.45)
PaO <sub>2</sub> /FiO <sub>2</sub> ratio	400–500	101 (73–151)	109 (77–154)	109 (74–186)	151 (86–223)	167 (122–258)
Tidal volume per kg of predicted body weight, mL/kg	NA	6.05 (5.78–6.75)	6.43 (5.97–6.95)	6.03 (5.73–6.81)	5.99 (4.82–7.39)	6.58 (5.66–7.02)
Plateau pressure, cmH <sub>2</sub> O	NA	24.00 (20.00–26.00)	20.00 (20.00–25.00)	21.00 (20.00–30.00)	25.00 (20.00–28.00)	22.00 (20.00–28.00)
PEEP, cmH <sub>2</sub> O	NA	8.00 (6.00–10.00)	10.00 (8.00–12.00)	10.00 (7.00–10.00)	8.00 (6.00–10.00)	5.00 (5.00–8.00)
Lung compliance, mL/cmH <sub>2</sub> O	60–100	30.00 (20.50–34.25)	30.00 (22.00–34.00)	27.00 (17.00–35.00)	30.00 (17.25–34.25)	30.00 (18.75–37.50)
Vasopressors	NA	30 (15.4%)	31 (17.4%)	31 (19.5%)	31 (25.0%)	21 (21.4%)
Lymphocyte count, 10 <sup>9</sup> /L	1.1–3.2	0.61 (0.39–0.86)	0.51 (0.32–0.77)	0.47 (0.33–0.78)	0.72 (0.38–1.07)	0.60 (0.23–1.07)
Platelet count, 10 <sup>9</sup> /L	125–350	161 (114–208)	160 (113–247)	141 (101–261)	161 (87–239)	141 (63–225)
Creatinine, mmol/L	64–104	74.0 (62.9–100.6)	76.6 (55.0–127.7)	67.6 (51.1–106.7)	60.4 (48.0–117.5)	75.7 (38.2–121.1)

Data are median (IQR) or n (%).

FiO<sub>2</sub> indicates fraction of inspired oxygen; NA, not available; PaCO<sub>2</sub>, partial pressure of carbon dioxide; PaO<sub>2</sub>, partial pressure of oxygen; PEEP, positive end expiratory pressure; SOFA, Sequential Organ Failure Assessment.



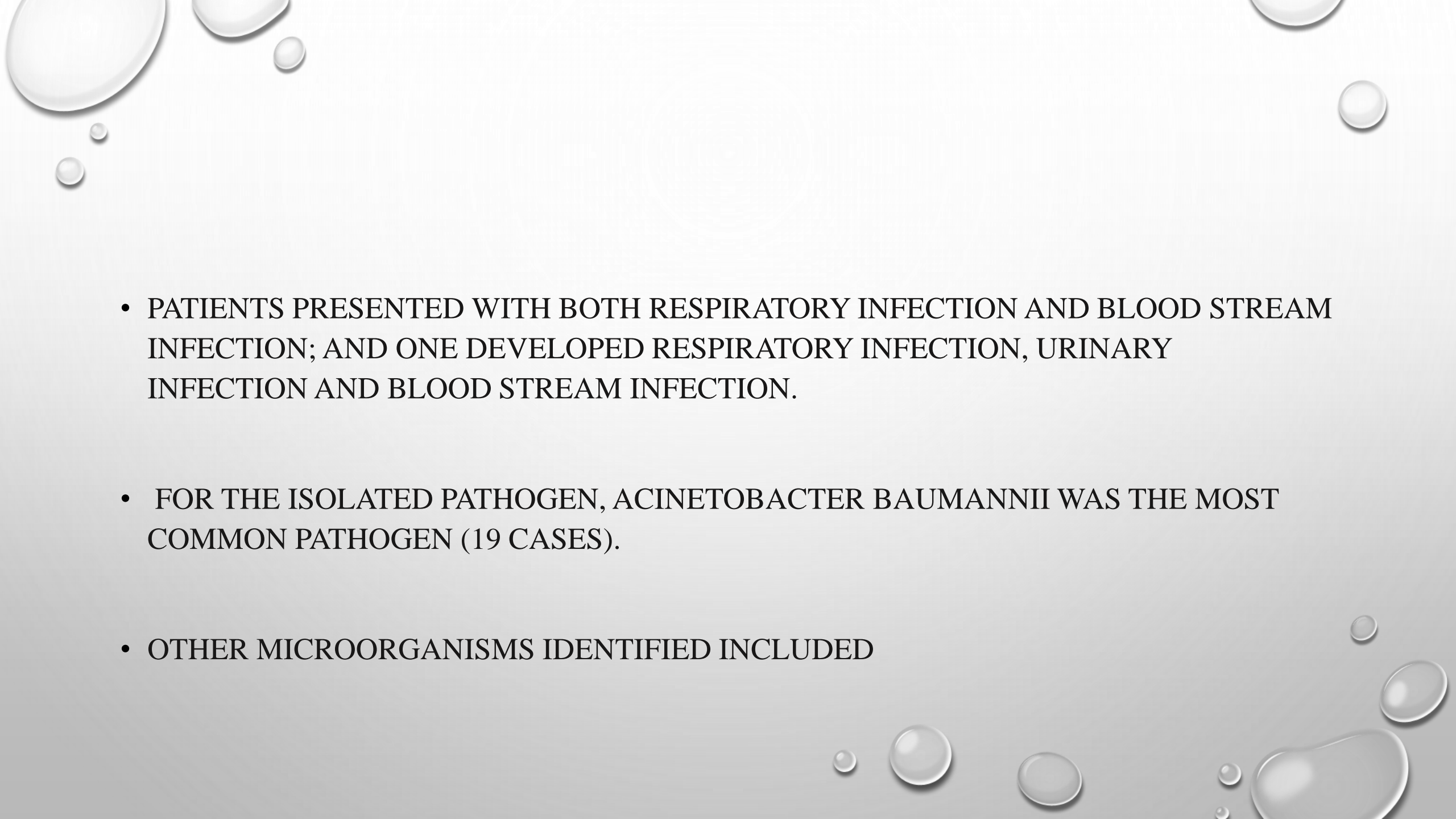
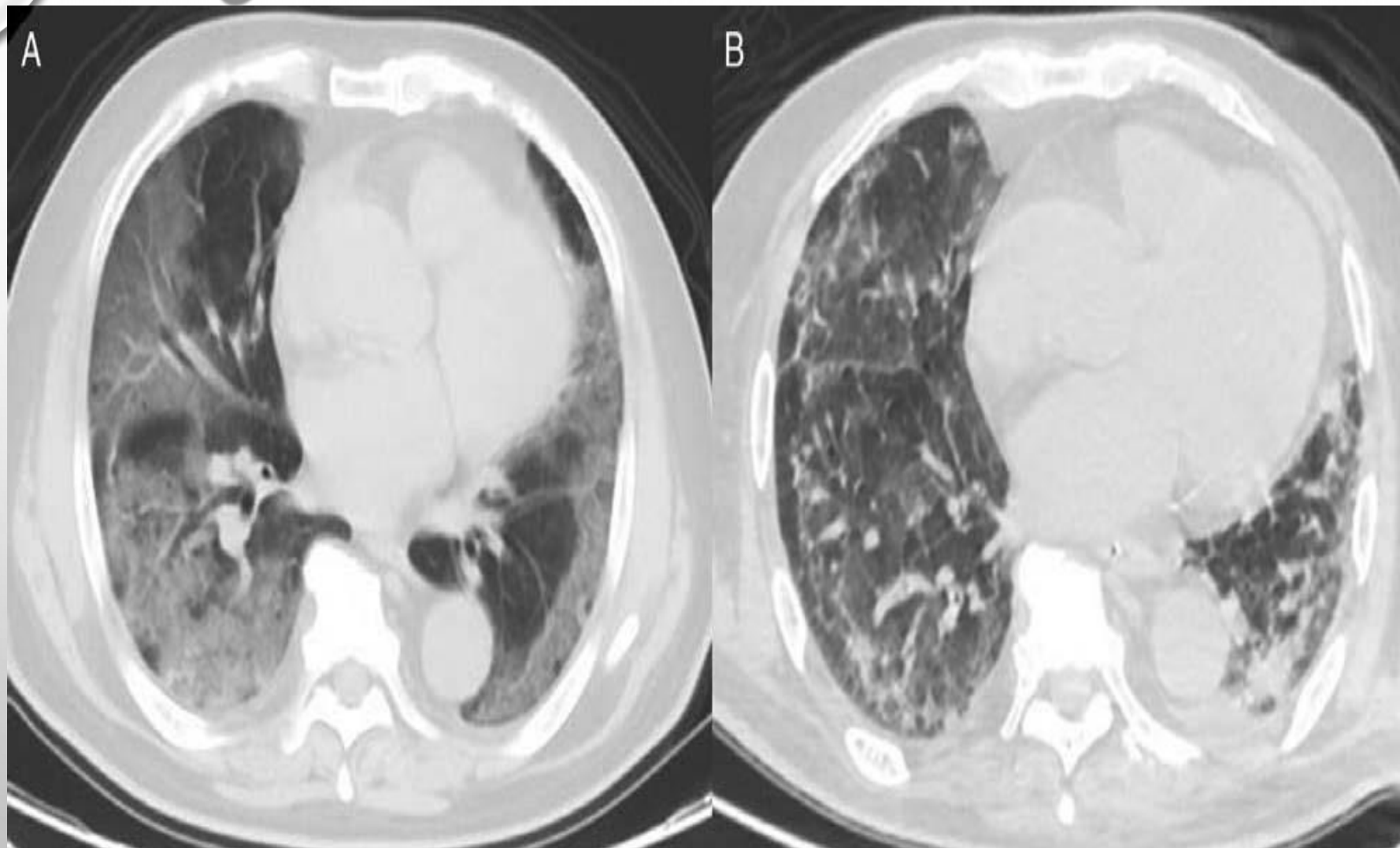
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- PATIENTS PRESENTED WITH BOTH RESPIRATORY INFECTION AND BLOOD STREAM INFECTION; AND ONE DEVELOPED RESPIRATORY INFECTION, URINARY INFECTION AND BLOOD STREAM INFECTION.
  - FOR THE ISOLATED PATHOGEN, ACINETOBACTER BAUMANNII WAS THE MOST COMMON PATHOGEN (19 CASES).
  - OTHER MICROORGANISMS IDENTIFIED INCLUDED

FIG. 2. Organ dysfunction of 195 critically ill COVID-19 patients during the first 3 weeks after critical illness onset. PaO<sub>2</sub> indicates partial pressure of oxygen; PaCO<sub>2</sub>, partial pressure of carbon dioxide; FiO<sub>2</sub>, fraction of inspired oxygen; PEEP, positive end expiratory pressure. \*P< 0.05 for survivors versus no



- CANDIDA ALBICANS (SIX CASES), ENTEROCOCCUS FAECALIS (FOUR CASES), KLEBSIELLA PNEUMONIAE (TWO CASES), COAGULASE-NEGATIVE STAPHYLOCOCCUS (ONE CASE), ESCHERICHIA COLI (ONE CASE), HEMOPHILUS INFLUENZA (ONE CASE), AND CORYNEBACTERIUM STRIATUM (ONE CASE).



# TREATMENT AND OUTCOME

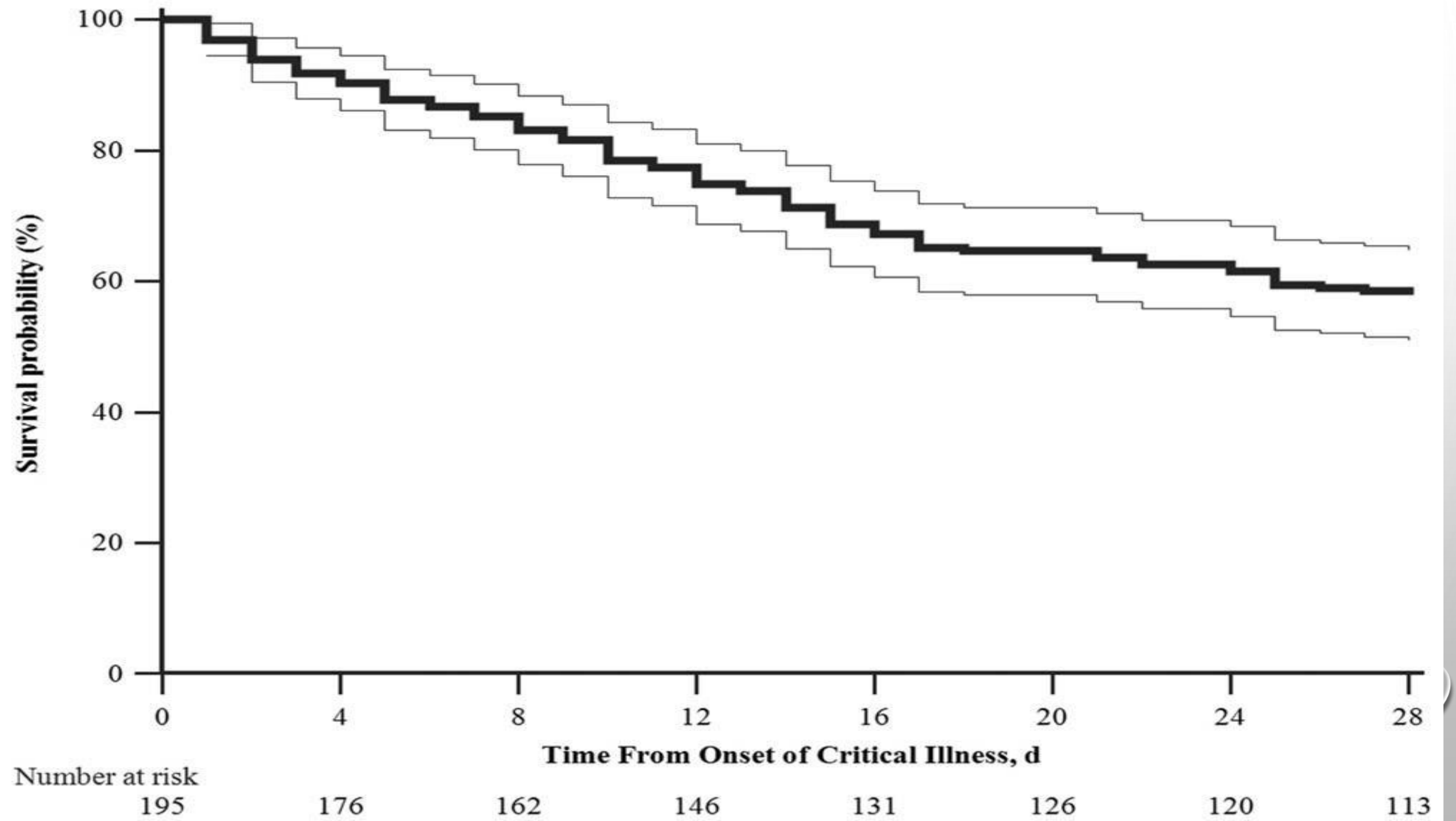
- AMONG THE 195 CRITICALLY ILL PATIENTS, 181 (92.8%) WERE MECHANICALLY VENTILATED, WHICH INCLUDED 84 (43.1%)
  - NONINVASIVELY AND 97 (49.7%) INVASIVELY. AMONG THE 97 INVASIVELY MECHANICAL VENTILATED PATIENTS, 28 (28.9%) RECEIVED PRONE VENTILATION, 57 (58.8%) RECEIVED NEUROMUSCULAR BLOCKED THERAPY, AND 22 (11.3%) RECEIVED TRACHEOSTOMY BECAUSE OF PROLONGED MECHANICAL VENTILATION. ON DAY 28, 41 (42.3%) OF 97 INTUBATED PATIENTS SURVIVED.
- AMONG THE 41 SURVIVED PATIENTS, 36 WERE SUCCESSFULLY EXTUBATED AND FIVE WERE STILL ON VENTILATORS ON DAY 28.

- THE GENERAL WARD BECAUSE OF A SHORTAGE OF ICU BEDS. ADDITIONALLY, 16 PATIENTS WITH SEVERE HYPOXEMIA RECEIVED EXTRACORPOREAL MEMBRANE OXYGENATION (ECMO) INCLUDING FIVE WHO DIED, FOUR WHO RECOVERED AND WERE DISCHARGED, THREE WHO WERE ON ECMO, THREE WHO WERE ON MECHANICAL VENTILATION, AND ONE WHO WAS TRANSFERRED TO THE WARD.
- AMONG THE 58 PATIENTS WITH AKI, 26 PATIENTS (44.8%) RECEIVED CRRT. FOR THE 26 PATIENTS WHO RECEIVED CRRT, 13 PATIENTS DIED WITHIN 28 DAYS. MOST PATIENTS RECEIVED ANTIVIRUS THERAPY (76.9%) AND GLUCOCORTICOIDS (71.3%).
- FIG. 4. SURVIVAL CURVES OF 195 CRITICALLY ILL PATIENTS WITH COVID-19. GRAY LINES REPRESENT 95% CONFIDENCE INTERVALS. COVID-19 INDICATES CORONAVIRUS DISEASE 2019.

TABLE 3. Clinical course and outcomes for 195 critically ill patients with COVID-19  
 Data are median (IQR) or n (%).

All patients (n = 195)

28-day mortality	82 (42.1)
Location of patients at 28 days	
Intensive care unit	19 (9.7)
Hospital ward	46 (23.6)
Home	48 (24.6)
Time course of illness, day	
Symptom onset to hospital admission	
Symptom onset to ICU admission	7.00 (5.00–10.00) 10.00 (7.00–15.00)
Symptom onset to discharge	24.00 (16.00–31.00)
Symptom onset to death	19.00 (14.00–27.75)
ICU length of stay Discharged patients	
Non-survivors	11.00 (6.50–19.50) 10.00 (6.25–15.00)
Duration of ventilation Discharged patients	
Non-survivors	10.00 (5.00–20.75) 8.00 (5.00–15.00)




Most nosocomial infections occurred in weeks 2 and 3. Nosocomial infection was noted in 55 cases (28.2%). The sites of infection include lungs (52 cases), blood stream (10 cases), and urinary tract (four cases). Among of the 55 cases, two patients presented both respiratory infection and urinary patient present with both infection; eight respiratory infection and blood stream infection and one developed respiratory infection



- VIRAL LOAD AND DEATH

- WE TRACKED THE PCR RESULTS OF 195 CRITICALLY ILL PATIENTS. FOR THE 113 SURVIVORS, THE TIME TO SARS-COV-2 RNA CLEARANCE WAS 22.00 (IQR 14.00–29.00) DAYS. AMONG THE 82 NON-SURVIVORS, 59 (72.0%) DIED WITH POSITIVE PCR RESULTS. IN ZHONGNAN HOSPITAL AND XISHUI PEOPLE'S HOSPITAL, PCR TESTS OF 16 DISCHARGED PATIENTS AND 23 DEATHS AS OF JANUARY 14, 2020 ARE SHOWN IN FIGURE 5. PCR RESULTS TURNED NEGATIVE FROM DAY 1 TO DAY 20 AFTER ILLNESS ONSET IN MOST SURVIVORS. MOST NON-SURVIVORS DIED WITH POSITIVE PCR RESULTS. HOWEVER, DEATH STILL OCCURRED IN A FEW PATIENTS WITH SUSTAINED NEGATIVE PCR TESTS.



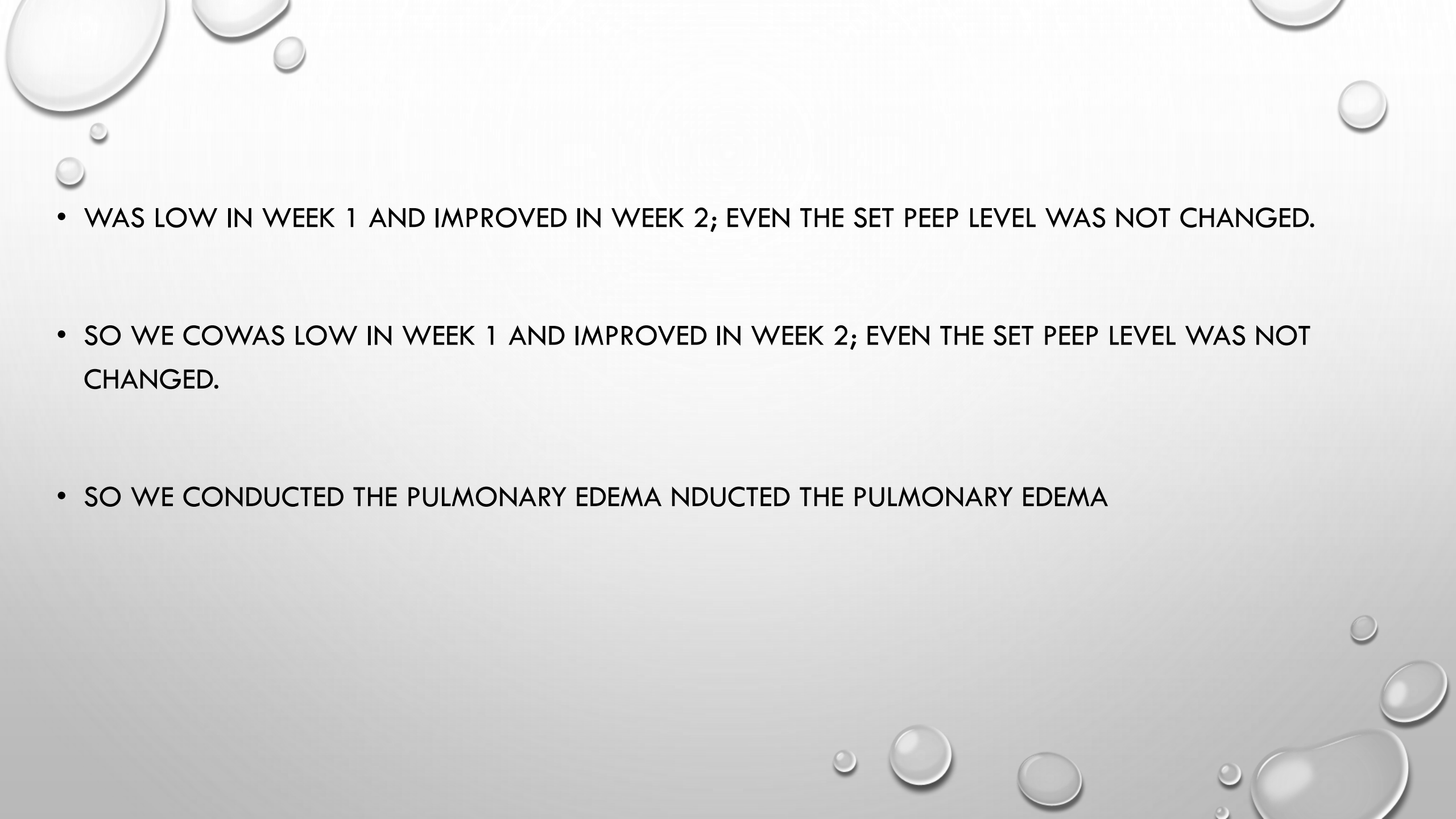


## •DISCUSSION

•THIS STUDY DEMONSTRATED THAT THE 28-DAY MORTALITY OF CRITICALLY ILL PATIENTS WITH COVID-19 WAS 42.1%. IN WEEK 1, CRITICALLY ILL COVID-19 WAS CHARACTERIZED WITH SHOCK AND HYPOXEMIA REQUIRING VASOPRESSORS AND A HIGH CONCENTRATION OF INSPIRED OXYGEN, INTUBATION OR EVEN ECMO. AS THE DISEASE PROGRESSED, LOW LUNG COMPLIANCE, HIGH DEAD SPACE, PULMONARY FIBROSIS, AND PULMONARY HYPERTENSION WERE NOTABLE. VIRAL INFECTION-INDUCED SEPTIC SHOCK WAS NOTABLE IN WEEK 1. ACUTE KIDNEY INJURY AND SECONDARY INFECTION WERE NOTABLE IN WEEK 3. A HIGH VIRAL LOAD WAS OBSERVED IN MOST NON-SURVIVORS.

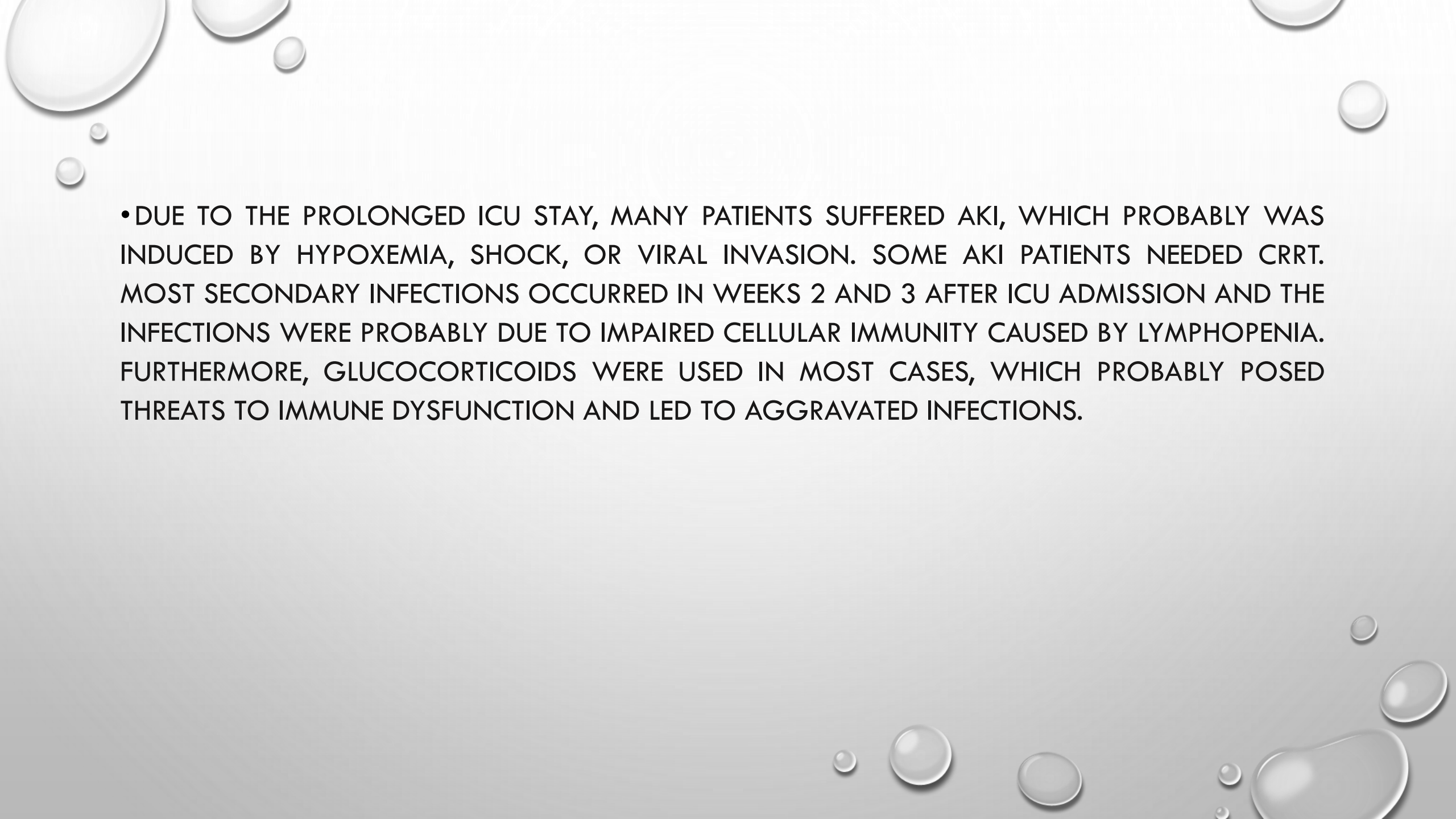
• ARDS WAS THE MOST NOTABLE COMPLICATION OF THE CRITICAL ILLNESS OF COVID-19. HEREIN, ARDS INDUCED BY SARS-COV-2 INFECTION MANIFESTED AS SEVERE HYPOXIA, HYPERVENTILATION IN THE EARLY PHASE (PRESUMED EXUDATION PHASE), WHICH PROGRESSED TO DEAD SPACE VENTILATION, HYPERCAPNIA, PULMONARY HYPERTENSION, AND POST-ARDS PULMONARY FIBROSIS (PRESUMED FIBROPROLIFERATIVE PHASE). PULMONARY HYPERTENSION AND DILATED RIGHT HEART, A HALLMARK OF ACUTE COR PULMONALE, WERE IDENTIFIED IN SOME ENROLLED CASES. THE INCIDENCE OF ACUTE COR PULMONALE IN OUR PATIENTS WAS PROBABLY UNDERESTIMATED BECAUSE NO RIGHT HEART CATHETERIZATION OR TRANSESOPHAGEAL ECHOCARDIOGRAPHY WAS AVAILABLE IN THE ISOLATION WARDS (14).



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- WAS LOW IN WEEK 1 AND IMPROVED IN WEEK 2; EVEN THE SET PEEP LEVEL WAS NOT CHANGED.
  - SO WE COWAS LOW IN WEEK 1 AND IMPROVED IN WEEK 2; EVEN THE SET PEEP LEVEL WAS NOT CHANGED.
  - SO WE CONDUCTED THE PULMONARY EDEMA NDUCTED THE PULMONARY EDEMA

- AND ARDS IMPROVED IN WEEK 2 FOR THE SURVIVORS. FOR THE NONSURVIVORS, THE  $PAO_2/FIO_2$  WAS STABLE AND SET PEEP LEVEL WAS DOWN IN WEEK 3.
- THIS ALSO IMPLIES THAT PERMEABILITY PULMONARY EDEMA IMPROVED IN WEEK 3.

- NOTABLY, IN THE PRESUMED EXUDATIVE STAGE OF ARDS (FIRST 2 WEEKS) INDUCED BY SARS-COV-2 INFECTION, HYPOXEMIA WAS SEVERE AND NEARLY ALL CRITICALLY ILL PATIENTS WERE ON MECHANICAL VENTILATION. USUALLY, VENTILATED PATIENTS REQUIRED SEDATION AND PARALYSIS TO REDUCE OXYGEN CONSUMPTION. LOW TIDAL VOLUME VENTILATION (4 ML/KG TO 8ML/KG PREDICTED BODY WEIGHT) AND TARGETED PLATEAU PRESSURE 30CMH<sub>2</sub>O WAS FOLLOWED. LOW COMPLIANCE WAS SEEN AT ALL TIMES. PRONE POSITIONING WAS USED TO IMPROVE OXYGENATION EFFICIENCY. ECMO WAS USED AS A RESCUE THERAPY FOR PATIENTS WHOSE GAS EXCHANGE COULD NOT BE SATISFIED BY MECHANICAL VENTILATION (15).



- DUE TO THE PROLONGED ICU STAY, MANY PATIENTS SUFFERED AKI, WHICH PROBABLY WAS INDUCED BY HYPOXEMIA, SHOCK, OR VIRAL INVASION. SOME AKI PATIENTS NEEDED CRRT. MOST SECONDARY INFECTIONS OCCURRED IN WEEKS 2 AND 3 AFTER ICU ADMISSION AND THE INFECTIONS WERE PROBABLY DUE TO IMPAIRED CELLULAR IMMUNITY CAUSED BY LYMPHOPENIA. FURTHERMORE, GLUCOCORTICOIDS WERE USED IN MOST CASES, WHICH PROBABLY POSED THREATS TO IMMUNE DYSFUNCTION AND LED TO AGGRAVATED INFECTIONS.

- HEREIN, THE RELATION BETWEEN VIRAL LOAD AND POOR OUTCOME IN CRITICALLY ILL PATIENTS WAS FIRST REPORTED. MOST NON-SURVIVORS DIED WITH POSITIVE RT-PCR RESULTS, WHICH INDICATED THAT MOST DEATHS IN CRITICAL ILLNESS WERE DIRECTLY RELATED TO VIRUS REPLICATION IN VIVO. INTERESTINGLY, THE RT-PCR TESTS TURNED NEGATIVE BEFORE DEATH IN SEVERAL NON-SURVIVORS. THIS MEANS THAT DEATHS WERE NOT RELATED TO HIGH VIRAL LOADS IN THESE CASES BUT MAY BE ASSOCIATED WITH MULTI-ORGAN DYSFUNCTION INDUCED BY INITIAL VIRAL INSULT

• THIS STUDY HAS LIMITATIONS. FIRST, PATIENTS WERE ISOLATED IN THE ICU WARD, WHERE PULSE CONTOUR CARDIAC OUTPUT ANALYSIS (PICCO), ULTRASONIC INSTRUMENTS, AND COMPUTED TOMOGRAPHY SCANS WERE IN SHORTAGE OR NOT AVAILABLE. A LOT OF DATA ABOUT THE HEMODYNAMIC VALUES AND RADIOLOGIC FINDINGS WERE ABSENT. THE EXUDATION PHASE AND FIBROPROLIFERATIVE PHASE OF ARDS INDUCED BY THE SARS-COV-2 INFECTION WERE PRESUMED. SECOND, DATA WAS COLLECTED UP TO DAY 28 AFTER CRITICAL ILLNESS ONSET. FUTURE STUDIES SHOULD FOCUS ON 90-DAY MORTALITY OR MORBIDITY AMONG SURVIVORS. THIRD, SARS-COV-2 RNA IN THE UPPER AIRWAY WAS NOT DETECTED REGULARLY IN OUR CASES.



# CONCLUSIONS

- THE MORTALITY OF CRITICALLY ILL PATIENTS WITH COVID-19 WAS HIGH. ARDS AND SHOCK WERE NOTABLE IN THE CLINICAL COURSE OF THE CRITICAL ILLNESS.
- VENTILATION SUPPORT AND HEMODYNAMIC SUPPORT WERE THE CORNERSTONES FOR CRITICAL CARE.
- A HIGH VIRAL LOAD WAS ASSOCIATED WITH THE DEATH OF CRITICALLY ILL COVID-19 PATIENTS.



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