sciendo

PROCEEDINGS OF THE LATVIAN ACADEMY OF SCIENCES. Section B,
Vol. 76 (2022), No. 3 (738), pp. 338–345.

DOI: 10.2478/prolas-2022-0051

CLINICAL CHARACTERISTICS OF INVASIVELY VENTILATED COVID-19 PATIENTS: AN OVERVIEW OF CLINICAL EXPERIENCE IN PAULS STRADIŅŠ CLINICAL UNIVERSITY HOSPITAL, RĪGA, LATVIA

Paula Zviedre[1,2,#], Darja Smirnova[1,2], Anna Klēšmite[1,2], Elīna Žuka[2], Elīna Romanovska[2], Ģirts Freijs[1], and Oļegs Sabeļņikovs[1,2]

[1] Department of Anaesthesiology and Intensive Care, Pauls Stradiņš Clinical University Hospital, 13 Pilsoņu Str., Rīga, LV-1002, LATVIA

[2] Rīga Stradiņš University, 16 Dzirciema Str., Rīga, LV-1007, LATVIA

[#] Corresponding author, paulazviedre@gmail.com

Communicated by Modra Murovska

This retrospective single-centre study was conducted in an intensive care unit (ICU) in Pauls Stradiņš Clinical University Hospital (Rīga, Latvia) between 1 October 2020 and 30 April 2021. The aim was to assess the baseline clinical characteristics and their association with outcome for critically ill coronavirus disease 2019 (COVID-19) patients admitted to the ICU and requiring invasive mechanical ventilation (IMV). Demographic, clinical, laboratory, length-of-stay and mortality data were collected from medical records. In total, 66 critically ill patients admitted to the ICU were enrolled in this study. 77% were male, and the median age was 65.5 [57.0–70.8] years. Comorbidities included obesity (67.2%), cardiovascular disease (63.6%) and type II diabetes (38.1%). Prone positioning was performed in most cases (68.2%) and one-third (34.8%) of patients required renal replacement therapy during their stay in the ICU. The median time to intubation after hospitalisation was eight [3.3–10.0] days. The median length-of-stay in the ICU was 12 [6.0–18.5] days and the overall mortality among all invasively ventilated patients in the ICU was 86%. In survivors, the duration of time between the onset of symptoms and hospitalisation, and time between the onset of symptoms and intubation, were found to be shorter than in non-survivors.

Keywords: *SARS-CoV-2, invasive mechanical ventilation, intensive care unit, mortality.*

INTRODUCTION

In December 2019, Wuhan (China) reported a series of cases of acute respiratory failure caused by a new aggressive strain of coronavirus, SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2). The virus rapidly spread worldwide and evolved into a pandemic very soon. It reached Latvia in early Spring of 2020, when around fifty patients were hospitalised due to acute respiratory failure caused by the novel coronavirus. However, an alarming spike in Coronavirus Disease 2019 (COVID-19) cases hit the central region of Latvia in October (ECDC, 2021). New cases were reported with dynamic progression. Hospitalisation and intensive care were required for a thousand COVID-19 patients. The situation was aggravated by the fact that a predominant number of patients were hospitalised in two main tertiary care hospitals in Rīga with the total intensive care unit (ICU) capacity of approximately 80 hospital beds. Furthermore, these ICUs usually had an up to 80% occupancy during the winter months.

The clinical spectrum of SARS-CoV-2 ranges from asymptomatic or mild cases to a critical disease with acute respiratory failure. Previous reports (Grasselli, 2020; Hong *et al*., 2020; Immovilli, 2020; Langer *et al*., 2021) showed that, on average, one quarter of patients hospitalised with COVID-19 required admission to an intensive care unit and at least half of them required invasive mechanical ventilation (IMV) (Di Lecce *et al*., 2020; Grasselli, 2020; Wang *et al*., 2020; Lang *et al*., 2021). Baseline characteristics reported

for most ICU patients were obesity, diabetes, hypertension, and cardiovascular disease (Hajjar *et al*., 2021). The overall ICU mortality varied widely: from 16% to 88%, depending on patient and healthcare system characteristics, with an invariably higher mortality rate in the invasively ventilated patient group (Grasselli *et al*., 2020; Huang *et al*., 2020; Wei-jie, 2020; Lang *et al*., 2021; Zanella *et al*., 2021).

Data available so far have shown a high mortality rate among invasively ventilated COVID-19 patients worldwide, thus, possible risk factors for poor outcomes need to be analysed to identify strategies for individual case management and mortality reduction. Therefore, knowledge of the main clinical characteristics and outcomes of critically ill COVID-19 patients is determinative for health care organisation during the pandemic.

We aim to identify the defining demographic, clinical and laboratory characteristics, treatment strategies, and their association with outcome in critically ill COVID-19 patients admitted to the ICU in Pauls Stradiņš Clinical University Hospital in Rīga, Latvia, during the first wave of the pandemic.

MATERIALS AND METHODS

Study design and population. This retrospective single-centre study was conducted in an ICU in Pauls Stradiņš Clinical University Hospital between 1 October 2020 and 30 April 2021. Patients corresponding with the inclusion criteria were enrolled in the study. The inclusion criteria were defined as: 1) age over 18 years; 2) laboratory-confirmed SARS-CoV-2 infection; 3) moderate or severe acute respiratory distress syndrome (ARDS); 4) admission to the ICU due to respiratory failure; and 5) invasive mechanical ventilation provided for at least 72 hours. Patients who died within the first 72 hours after the admission to the ICU, and patients who did not require invasive mechanical ventilation, were excluded from this study. During the observation period, twenty patients admitted to our ICU with COVID-19 died within the first 72 hours of initiating invasive mechanical ventilation, and most of them died within the first 24 hours of initiating IMV. Four of them had known underlying diseases that were very likely to be the direct cause of death, such as orfarin overdose, pulmonary embolism, unrelated sepsis, and terminal malignancy. Another sixteen patients deteriorated very rapidly from pneumonia. We chose to exclude these patients for two reasons — to have a more homogenous study population, and because we initially planned on including and analysing data on ventilator settings, which would have required at least 72 hours of recorded ventilator parameters. Pregnancy was also considered an exclusion factor from the study to have a more homogenous population. Furthermore, the exclusion of pregnant patients is a standard practice in similar studies. However, during the observation period, no pregnant patients with COVID-19 required intensive care and invasive mechanical ventilation.

Laboratory confirmation of SARS-CoV-2 infection was obtained from a positive result of real-time reverse transcriptase-polymerase chain reaction (RT-PCR) assay on nasal and pharyngeal swabs. In some cases, confirmation with reverse transcriptase–polymerase chain reaction assay from lower respiratory tract aspirates was performed. The severity stages of acute respiratory failure were classified by the Berlin definition for ARDS: mild, with partial pressure of oxygen (PaO_2) and fraction of inspired oxygen (FiO_2) ratio ($PaO_2/FiO_{2)}$ less than or equal to 300 mmHg but greater than 200 mmHg; moderate, with PaO_2/FiO_2 less than or equal to 200 mmHg but greater than 100 mmHg; and severe, with PaO_2/FiO_2 less than or equal to 100 mmHg (Ranieri *et al*., 2012).

According to the local pandemic plan, COVID-19 patients were treated at different ICUs — Respiratory Intensive Care Unit (RICU), where patients with moderate to severe respiratory failure were treated with non-invasive respiratory support, and General Intensive Care Unit (GICU), where patients with severe and rapidly deteriorating ARDS were admitted, showing clinical signs and symptoms that did not allow a non-invasive respiratory support approach, and usually requiring prompt intubation, as well as patients requiring continuous renal replacement therapy (CRRT) or veno-venous extracorporeal membrane oxygenation (vvECMO). RICU and GICU were located in the same building of the hospital. Patients were admitted to the GICU from the following locations: the emergency room (ER); the RICU; other primary and secondary care hospitals; other tertiary care hospitals (as our centre is exclusive for providing extracorporeal membrane oxygenation (ECMO) procedures).

Data collection. The study was conducted in accordance with the ethical standards of the Declaration of Helsinki. Participants of the study were admitted to hospital between 1 October 2019, and 30 April 2020. Clinical data reported in this study were collected from electronic and paper-based medical records (clinical charts, nursing records, laboratory findings). The collected data included the following: demographic statistics (age, gender, body mass index (BMI), comorbidities); epidemiological data (time of symptom onset prior to hospitalisation, where the time of disease onset was defined as the day when the first symptoms appeared); laboratory findings of inflammatory response and "cytokine storm" (leukocytosis status, level of procalcitonin (PCT), C-reactive protein (CRP), ferritin and lactate dehydrogenase (LDH)); mode of respiratory support (invasive mechanical ventilation or non-invasive mechanical ventilation); invasive respiratory support parameters (level of positive end-expiratory pressure (PEEP); arterial partial pressure of oxygen (PaO_2) and fraction of inspired oxygen (FiO_2) ratio (PaO_2/FIO_2 ratio); the use of CRRT and ECMO; prone positioning strategy; and pharmacological treatment strategy (neuromuscular blocking agents, corticosteroids, low-molecular-weight-heparin (LMWH), vasoactive agents for haemodynamic support, and antiviral agents).

The Sequential Organ Failure Assessment (SOFA) score was determined for patients on the day of admission to hos-

pital, and on the day of admission to the ICU. The duration of time from the onset of disease to admission to the hospital, to admission to the ICU, and to initiation of invasive mechanical ventilation, were recorded.

Finally, the following patient outcomes were recorded: ICU mortality and the total ICU length of stay.

Statistical analysis. Categorical variables are reported as frequencies (percentages with 95% confidence interval (CI)) and compared by the χ^2 test or Fisher's exact test, as appropriate. Continuous variables were expressed as mean (with standard deviation (SD)) or median (with interquartile range (IQR) and 95% CI) according to distribution and compared using independent group t-tests for the data with normal distribution. Otherwise, the Mann–Whitney U test was used.

The association of risk factors with time to death was assessed by univariable and multivariable Cox proportional hazards regression models; Hazard ratios (HR) were expressed per unit of change in the corresponding variable. A two-sided α of less than 0.05 was considered statistically significant.

All statistical analyses were performed using the International Business Machines (IBM) Corporation Statistical Package for the Social Sciences (SPSS) version 25.0 software (SPSS Inc).

RESULTS

From 1 October 2020 to 30 April 2021, 66 consecutive critically ill patients who fit all inclusion criteria were enrolled in this study (Fig. 1). Table 1 shows the baseline characteristics of the patients. Overall, 77% (n = 55) of patients were male, and the median age was 65.5 (57.0–70.8) years. Most patients (n = 41; 67.2%) were obese, with a median body mass index of 32.2 (22.6–52.5). Twenty-eight

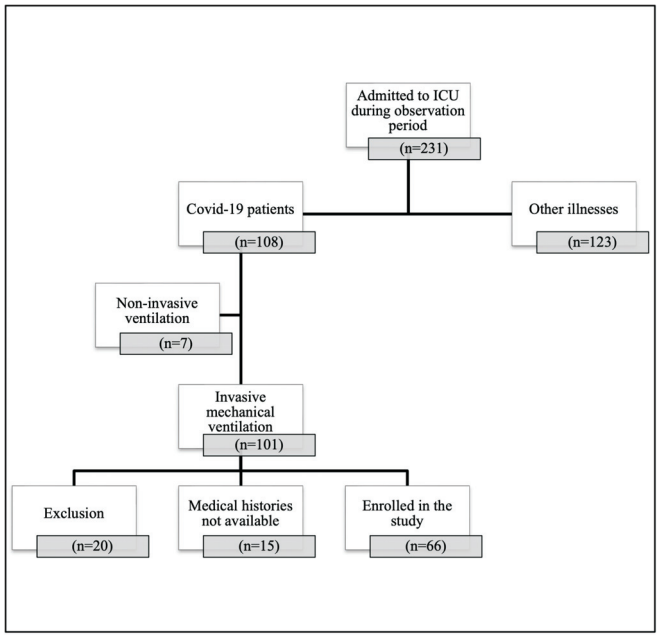

Fig. 1. Flow chart of the study.
ICU, Intensive care unit; n, number of patients.

Table 1. Demographics and baseline characteristics of critically ill 2019-nCoV patients

Patients, n	66
Gender, M/F (%)	77.3% / 22.7%
Age, years, median [IQR]	65.5 (57.0–70.8)
Male	62 (55.5–69.5)
Female	70 (66.0–72.0)
BMI, n (% of patients)	
25.0 to 29.9	25 (38%)
30.0 to 34.9	23 (35%)
35.0 to 39.9	12 (18%)
> 40,00	6 (9%)
Patients with at least one comorbidity, n (% of patients):	
Cardiovascular disease (hypertension):	42 (64%)
Diabetes type II	24 (38%)
Immunodeficiency (HIV, malignancy, prior transplantation)	13 (19%)
Respiratory disease	4 (6%)
Patients with at least 2 comorbidities, n (% of patients)	28 (42%)
ARDS upon admission to hospital, n (% of patients):	
Mild	10 (16.4%)
Moderate	15 (24.6%)
Severe	36 (59%)
ARDS before initiation of IMV, n (% of patients):	
Moderate	2 (3.1%)
Severe	64 (96.9)
NIV: CPAP or BiPAP, n (% of patients)	52 (78.8%)
IMV ventilation mode initiated after intubation, n (% of patients):	
SIMV PC+PS	42 (64%)
SIMV PRVC	15 (23%)
SIMV VC	5 (7%)
VC	4 (6%)
PEEP, cmH2O, median [IQR]	9.4 (8.0–10.0)
Received medication, n (% of patients):	
Remdesivir	23 (34.9%)
Cisatracurium	13 (19.7%)
Vasoactive agents	60 (90.9%)
CRRT, n (% of patients)	23 (34.9%)
Pronation, n (% of patients)	45 (68.2%)
Prone related complications, n (% of patients):	
Facial oedema	7 (15.6%)
Gastric retention	4 (8.9%)
Pressure sores	3 (6.7%)
Accidental extubation	1 (2.2%)
Hemodynamic instability	2 (4.4%)
Bacterial infection, n (% of patients)	32 (48.5%)
Time from symptom onset to, median (IQR):	
Hospitalisation	7 days (4.0–10.0)
Admission to ICU	12 days (9.0–16.0)
Initiation of IMV	15 days (11.0–17.0)
Clinical outcome, n (% of patients):	
Death in ICU	57 (86.4%)
Discharged alive from ICU	9 (13.6%)

ARDS, acute respiratory distress syndrome; BMI, body mass index; BPAP, bilevel positive airway pressure; cmH2O, centimetres of water column; CPAP, continuous positive airway pressure; CRRT: continuous renal replacement therapy; F, female; HIV, human immunodeficiency virus; ICU, intensive care unit; IMV, invasive mechanical ventilation; IQR, interquartile range; M, male; NIV, non-invasive ventilation; PC, pressure control; PEEP, positive end-expiratory pressure; PRVC, pressure regulated volume controlled; PS, pressure support; SIMV, synchronised intermittent mandatory ventilation; VC, volume control; 2019-nCoV, novel coronavirus.

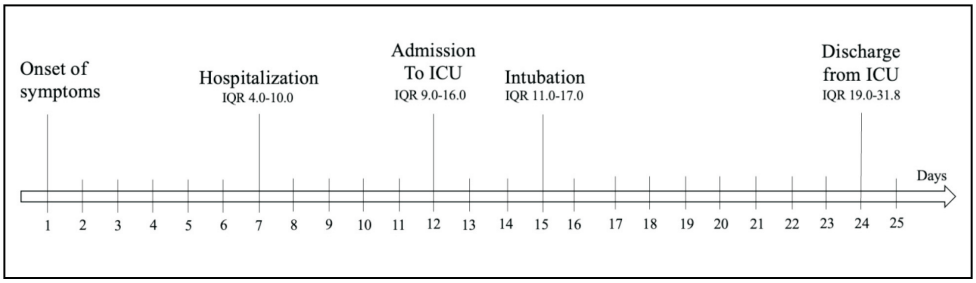

Fig. 2. Median timeline of COVID-19 disease.
ICU, Intensive care unit;
IQR, interquartile range.

(42.4%) patients had at least two other comorbidities, predominated by cardiovascular disease (mainly hypertension) (n = 42; 63.6%), and followed by type II diabetes (n = 24; 38.1%). Pulmonary or respiratory comorbidities were not commonly observed (n = 4; 6.0%).

The median time of onset of symptoms prior to hospitalisation and prior to admission to the ICU was 7 (4.0–10.0) and 12 (9.0–16.0) days, respectively. The median time to intubation after hospitalisation was 8 (3.3–10.0) days (Fig. 2).

Fifty-two (79%) patients received non-invasive mechanical ventilation (continuous positive airway pressure (CPAP) or biphasic positive airway pressure (BiPAP)) prior to intubation, and the median duration of non-invasive ventilation (NIV) was 71 (15.8–138.0) hours (min 1 hour and max 13 days).

Upon admission to the hospital, sixty-one of the patients (92.4%) met the criteria for ARDS, and more than half of them (n = 36; 59%) met the criteria for severe ARDS, with the median Pao_2/Fio_2 of 92 (63.5–172.3). The median SOFA score upon admission to the hospital and upon admission to the ICU was 3 (2.0–5.0) and 5 (4.0–7.0), respectively.

The vast majority of patients (n = 64; 96.9%) met the criteria for severe ARDS upon intubation, with the median Pao_2/Fio_2 of 57 (48.0–69.0). Following intubation and initiation of invasive ventilation, an increase of the mean Pao_2/Fio_2 was noted, with the median Pao_2/Fio_2 of 105.5 (69.5–142.0] at 24 hours after intubation. This was followed by a decrease, with the median Pao_2/Fio_2 of 99 (71.3–142.0) and 94.5 (68.3–147.0) at 48 and 72 hours after intubation, respectively (Fig. 3).

Prone positioning (PP) was performed in 68.2% (n = 45) of cases. The median time for initiation of prone position after intubation was 9 (3.0–21.8) hours with a clear tendency to decrease over the study period. The median duration of a PP session was 18 (16.0–20.0) hours per day. The median number of PP sessions within the first three days after intubation was three, and median cumulative time for all PP sessions was 53.5 hours (47.8–59.8) or 74.3% of the period studied. Oxygenation (Pao_2/Fio_2 ratio) was significantly improved in prone positioning (median Pao_2/Fio_2 before PP was 69 (55.0–80.8), and maximum achieved Pao_2/Fio_2 in PP was 133 (84.5–175.4), p 0.001). PP complications were documented in 17 cases (37.8%), predominated by facial oedema (n = 7; 15.6%), gastric retention (4; 8.9%) and pressure sores (3; 6.7%). Only one case of accidental extubation was recorded.

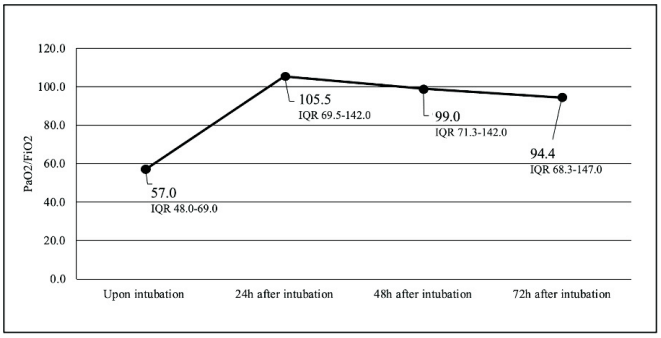

Fig. 3. Median PaO_2/FiO_2 ratio from intubation until the third day of invasive mechanical ventilation.
FiO_2, fraction of inspired oxygen; IQR, interquartile range; PaO_2, partial pressure of oxygen.

Regarding pharmacological treatment strategy, all patients underwent anticoagulation therapy with LWMH (mainly enoxaparin) at prophylactic or therapeutic doses, in accordance with evidence of D-Dimer increase or computed tomography (CT) signs of pulmonary embolism. After initiation of IMV, 20% of patients received a neuromuscular blocking agent (cisatracurium) to synchronise their breathing with the ventilator. Twenty-three patients (34.9%) were treated with Remdesivir. Finally, all patients were given systematic corticosteroids (dexamethasone), as required by local treatment protocol. Sixty (91%) patients required cardiovascular support with norepinephrine during their stay in the ICU.

Two veno-venous ECMO therapies were installed for patients who did not respond to conservative therapeutic efforts. One of the vvECMO patients survived and has gone through full rehabilitation. Twenty-three (34.8%) patients required continuous renal replacement therapy during their stay in the ICU. The median time for initiation of CRRT after admission to the ICU was 3 (2.0–8.0) days.

During hospitalisation, bacterial co-infection was identified in 35 (53%) patients, predominately caused by nosocomial pathogens. Superinfections were dominated by *Acinetobacter baumannii* (n = 19; 29%), *Staphylococcus epidermidis* (n = 12; 18%), *Streptococcus pneumoniae* (n = 9; 13%), *Staphyloccus hominis* (n = 8; 12%), *Pseudomonas aeruginosa* (n = 8; 12%) and *Klebsiella pneumonia* (n = 8; 12%). The findings from autopsy studies (n = 11) were consistent with changes associated with bacterial pneumonia.

Table 2. Baseline characteristics and univariate risk factors for outcome

	Overall	Survival	Non-survival	*p* value	Hazard ratio	CI 95%
Age, years, median [IQR]	65.5 (57.0–70.8) (n = 66)	61.2 (54.0–62.0) (n = 9)	62.4 (57.0-–71.0) (n = 57)	0.16	0.63	0.33–1.20
Male, n	51 (77.3%)	6 (66.7%)	45 (78.9%)	0.70	1.00	0.97–1.02
Female, n	15 (22.7%)	3 (33.3%)	12 (21.1%)			
BMI (kg/m^2), median [IQR]	31.0 (27.9–35.2)	34.3 (29.3–34.3)	30.9 (27.8–35.1)	0.48	0.98	0.94–1.03
Degree of obesity [min, max]:						
Overweight, BMI 25.0 to 29.9	25.0 (22.6–30.0) (38.0%)	3.0 (26.0–29.3) (33.3%)	22.0 (22.6–30.0) (38.6%)	0.73		
Class I obesity, BMI 30.0 to 34.9	23.0 (30.2–34.7) (34.8%)	3.0 (33.0–34.6) (33.3%)	20.0 (30.2–34.7) (35.1%)	0.27	1.83	0.62–5.36
Class II obesity, BMI 35.0 to 39.9	12.0 (35.1–38.7) (18.2%)	1.0 (35.5) (11.1%)	11.0 (35.1–38.7) (19.3%)	0.34	1.69	0.57–4.97
Class III obesity, BMI 40.0	6.0 (40.0–52.5) (9.1%)	2.0 (42.0–43.8) (22.2%)	4.0 (40.1–52.5) (7.0%)	0.29	1.86	0.59–5.88
Chronic comorbidities, n (% of patients):	48 (72.7%)	7 (77.8%)	41 (71.9%)	0.59	0.85	0.48–1.53
Hypertension	43 (63.6%)	4 (44.4%)	38 (66.7%)	0.43	1.25	0.72–2.17
Diabetes	24 (36.0%)	2 (25.0%)	22 (40.0%)	0.36	1.29	0.75–2.21

BMI, body mass index; CI 95%, 95% Confidence Interval; IQR, interquartile range.

Table 3. Clinical parameters upon admission to hospital and univariate risk factors for outcome

	Overall	Survival	Non-survival	*p* value	Hazard ratio	CI 95%
SOFA score [IQR]	3.0 [2.0–4.8]	2.0 [2.0-2.0]	3.0 [2.0-5.0]	0.89	1.01	0.90–1.13
PaO_2/FiO_2 upon hospitalisation, mmHg [IQR]	93.0 [64.8–168.3]	81.0 [55.0–107.0]	94.0 [67.0–171.0]	0.74	1.00	1.00–1.00
PaO_2/FiO_2 upon intubation, mmHg [IQR]	57.0 [48.0–69.0]	54.0 [47.3–65.3]	57.0 [50.0–69.0]	0.70	1.00	0.98–1.00
White blood cells, $10^3/\mu L$ [IQR]	7.7 [4.9–9.9]	9.0 [5.2–11.7]	7.6 [4.9–9.7]	0.36	0.97	0.89–1.04
C-reactive protein, mg/dL [IQR]	119.6 [76.9–243.4]	85.4 [72.1–253.6]	122.9 [78.7–235.4]	0.50	1.00	1.00–1.00
Procalcitonin, ng/mL [IQR]	0.2 [0.1–0.8]	0.1 [0.06–1.1]	0.2 [0.1–0.8]	0.48	0.91	0.71–1.18
LDH, U/L [IQR]	518.0 [380.3–622.0]	425.0 375.0–526.0]	522.0 [423.0–622.0]	0.70	1.00	1.00–1.00
D-dimer, ng/mL [IQR]	1.9 [0.9–2.9]	2 [1.0–6.3]	1.9 [0.9–2.7]	0.29	0.98	0.94–1.02
Ferritin, ng/mL [IQR]	831.0 [518.7–1270.0]	870.0 [626.2–1529.0]	813.0 [514.0–1246.0]	1.00	1.00	1.00–1.00

CI 95%, 95% confidence interval; FiO_2, fraction of inspired oxygen; IQR, interquartile range; LDH, lactate dehydrogenase; PaO_2, partial pressure of oxygen; SOFA, sequential organ failure assessment.

The median ICU length-of-stay was 12 (6.0–18.8) days (min 3 days and max 75 days) and the overall mortality among all invasively ventilated patients was 86%. 14% of enrolled patients survived and were discharged either to RICU, or to intensive care units in secondary care hospitals.

In the multivariable analysis, age, BMI, comorbidities, treatment strategy (pharmacological intervention, pronation or CRRT), as well as the Pao_2/Fio_2 ratio upon hospitalisation and upon intubation, were not found to be significant independent risk factors for increased mortality (Tables 2, 3, 4). Of all the parameters analysed, only two could be associated with increased mortality, as both showed statistical significance: time between the onset of first symptoms and admission to hospital ($p < 0.001$; HR 0.94), and time be-

Table 4. Treatment strategies, complications, and univariate risk factors for outcome

	Overall	Survival	Non-suvival	*p* value	Hazard ratio	CI 95%
Remdesevir, n (% of patients)	23 (34.8%)	3 (33.3%)	20 (35.1%)	0.26	1.37	0.79–2.37
Cisatracurium, n (% of patients)	13 (19.7%)	1 (11.1%)	12 (21.1%)	0.26	1.45	0.76–2.77
CRRT, n (% of patients)	21 (31.8%)	3 (33.3%)	18 (31.6%)	0.59	0.86	0.49–1.51
Prone positioning at least once, n (% of patients)	45 (68.2%)	6 (66.7%)	39 (68.4%)	0.98	1.01	0.57–1.77
Bacterial superinfection, n (% of patients)	32 (48.5%)	5 (55.6%)	27 (47.4%)	0.17	0.96	0.41–1.17

CI 95%, 95% Confidence Interval; CRRT, continuous renal replacement therapy.

Table 5. Timeline of disease progression and univariate risk factors for outcome

	Overall	Survival	Non-survival	*p* value	Hazard ratio	CI 95%
Time from onset of symptoms to hospitalisation, median days [IQR]	7.0 4.0–10.0	8.0 (4.0–9.5)	7.0 (4.0–10.0)	4.97×10^{-9}	0.94	0.87–1.00
Time from onset of symptoms to hospitalisation in ICU, median days [IQR]	12.0 (9.0–16.0)	9.0 (9.0–15.5)	12.0 (9.0–16.0)	0.24	0.98	0.94–1.02
Time from onset of symptoms to intubation, median days [IQR]	15.0 (11.0–17.0)	11.0 (8.0–14.0)	15.0 (12.0–17.0)	4.74×10^{-9}	0.90	0.87–0.93
ICU length of stay, median days [IQR]	12.0 (6.0–18.8)	45.0 (31.0–57.0)	9.0 (6.0–15.0)	0.37	0.98	0.94–1.02

CI 95%, 95% confidence interval; ICU, intensive care unit; IQR, interquartile range.

tween the onset of first symptoms and intubation, ($p < 0.001$; HR 0.90) (see Table 5).

DISCUSSION

In this study we present baseline demographic, clinical, and treatment characteristics, and their relationship with ICU mortality of critically ill patients with laboratory-confirmed SARS-CoV-2, who were admitted to the ICU during the first wave of the pandemic. Taking into consideration the relatively high mortality observed in this study, it seems particularly important to analyse the demographic and clinical characteristics of the critically ill COVID-19 patients enrolled.

The majority of the patients in this study were male (n = 52, 77%) with a median age of 65.5 (57.0–70.8) years. The median age was markedly higher in female patients — 70 (66.0–72.0) years, thus leading to the hypothesis that COVID-19 favours younger male patients. However, age and gender were not found to be significant independent risk factors for increased mortality in our study ($p = 0.16$ and $p = 0.7$, respectively).

The demographic data and common comorbidities were similar to other published international reports with the predominance of hypertension, obesity and diabetes, and a relatively small percentage of patients with previous chronic pulmonary disease (Di Lecce *et al*., 2020; Grasselli, 2020; Grasselli *et al*., 2020; Immovilli, 2020; Wang *et al*., 2020). The prevalence of such comorbidities as hypertension and diabetes was slightly higher in the population of our study, reaching 63.6% and 36%, respectively (Di Lecce *et al*., 2020; Immovilli, 2020; Lang *et al*., 2021; Zanella *et al*., 2021).

Median BMI reported in our study was higher, when compared to two large multicentre study reports from 24 Italian ICUs (Graselli *et al*., 2020; Zanella *et al*., 2021). We consider that this finding can be described by the difference in BMI between these two populations (Eurostat, 2019).

The median time of admission to the ICU and initiation of invasive mechanical ventilation were similar to reports from previous studies in other European countries and China (Grasselli *et al*., 2020; Wei-jie, 2020). Nevertheless, the overall mortality was higher, as only very severe ARDS patients (often requiring prompt intubation after admission to the ICU) were enrolled in our study. This finding supports the common clinical knowledge that the need for invasive mechanical ventilation is associated with more severe condition with a higher risk of adverse outcome.

Strategies like prone positioning and CRRT were also implemented, with similar frequency as reported in previous studies. Prone positioning was applied at the discretion of intensivists, most often as a rescue therapy when lower PaO_2/FiO_2 ratios were observed. Accordingly, this would mean that prone positioning was applied to patients with worse disease severity, explaining the clinical outcomes for patients in the PP group. Nevertheless, there was a statistically significant improvement of oxygenation in prone positioning ($p < 0.001$), as previously observed (Langer *et al*., 2021; Lang *et al*., 2021).

SARS-CoV-2 infection is still a relatively novel disease, and current treatment guidelines are continuously changing and being updated. At the time of the study period, no spe-

cific treatment was recommended for coronavirus infection, except for scrupulous symptomatic and supportive treatment. Nevertheless, abnormal cytokine production and regulation had been observed in COVID-19 patients. This so-called "cytokine storm" was associated with disease severity, being the leading factor responsible for the deterioration and even death (Liu *et al*., 2021). Thus, patients with severe COVID-19 can develop a systemic inflammatory response leading to multisystem organ dysfunction (Hong *et al*., 2020; Huang *et al.,* 2020). Therefore, the use of corticosteroids (dexamethasone) was routinely prescribed for the patients in our study, in the hopes that anti-inflammatory effects of this medication would diminish the damaging effects at the early stages of cytokine storm. This approach was based on reports indicating that the use of corticosteroids resulted in lower serum cytokine concentrations (Hong *et al.*, 2020). Furthermore, 34.8% of patients received remdesivir as a specific antiviral agent. However, in this study, no effective outcomes were observed in the use of aforementioned pharmacological agents.

The disastrous course of COVID-19 is further emphasised by the fact the mortality rate in this study was much higher than commonly described for a general ARDS population (with a 60-day survival of 68%). ARDS mortality is generally lower in tertiary care hospitals, compared to primary or secondary care hospitals (Máca *et al.*, 2017; Raymondos *et al.*, 2017), such as the one this study was conducted in.

The overall mortality rate of 86% can be at least partially explained by the relatively high age of our population. It has been reported in previous studies that older age is an important independent predictor of mortality in SARS (severe acute respiratory syndrome) and MERS (Middle East respiratory syndrome) infections, and there have been suggestions that older age might also be associated with higher death rate in patients with COVID-19 (Zhou, 2020).

In the present study, the factors showing statistical significance regarding increased mortality were the duration of time between the onset of symptoms and admission to the ICU; and the duration of time between the onset of first symptoms and intubation. This corresponds with the results of other publications, showing statistically significant negative correlations between fatality rate and ICU admission rate, and stressing the need for timely increase in ICU surge capacity to ensure that an ICU bed is available for every patient who requires one (Grasselli, 2020; Immovilli, 2020).

LIMITATIONS

Our study has several limitations, mainly due to the retrospective observational nature of this study. Firstly, data were mainly collected from medical records, thereby no tests were made specifically for the study purposes only; thus, some variables have missing data. We have not collected information about specific ventilatory parameters (such as driving pressure, plateau pressure and respiratory system compliance) that seem to have effect on COVID-19 disease outcome, as described in some later publications (Sabaka *et al.*, 2021; Tonetti *et al.*, 2021). As this study was conducted during the first COVID-19 wave, no unified ventilation protocol had been developed in our department yet. Hence, the choice of ventilation mode and parameters was largely dependent on each clinician's judgement. When retrieving the data, we found that, initially, not all parameters of interest were regularly recorded, which, unfortunately, led to incomplete information on these characteristics. This could be explained by the period of a relative overload of work attributed to the sudden influx of critically ill COVID-19 patients. Moreover, some laboratory variables (for instance, Interleukine-6 (Il-6)) had also not been tested in the earliest admission cases, as the significance of some laboratory variables, including Il-6 as a predictor for clinical outcome, was highlighted in later publications (Ranieri *et al.*, 2012; Puah *et al.,* 2021).

Secondly, our study population consisted of consecutive adult patients with laboratory-confirmed COVID-19 infection, who were admitted to the ICU due to moderate or severe ARDS, so we cannot exclude high heterogeneity among viral load, comorbidities, and fragility of enrolled patients.

Thirdly, the results of our research can be attributed only to critically ill COVID-19 patients with rapid deterioration of ARDS, requiring prompt initiation of invasive mechanical ventilation upon admission to the ICU in almost all cases. We have not compared clinical outcomes among invasively ventilated and non-invasively ventilated severe COVID-19 patients. Because of the selected study population, the overall ICU mortality was higher, when compared to data from other studies (Di Lecce *et al.*, 2020; Graselli *et al.*, 2020).

CONCLUSION

This retrospective study reported a clinical experience in a tertiary care ICU in Rīga, Latvia, during first wave of the pandemic caused by novel coronavirus SARS-CoV-2. In this population of 66 critically ill patients with laboratory-confirmed COVID-19 admitted to the ICU, the median ICU length-of-stay was 12 days and the overall mortality among all invasively ventilated patients was 86%. Compared with the non-survivors, the survivors had shorter duration of time between the onset of symptoms and hospitalisation, and shorter duration of time between the onset of symptoms and initiation of invasive mechanical ventilation.

ACKNOWLEDGEMENTS

The publishing of this study is funded by the Society of Anaesthesiologists and Reanimatologists of Latvia. We acknowledge all health-care personnel involved in the diagnostics and treatment of patients in the Intensive Care Unit of Pauls Stradiņš Clinical University Hospital in Rīga, Latvia.

REFERENCES

Di Lecce, V., Carpagnano, G. E., Pierucci, P., Quaranta, V. N., Barratta, F., Zito, A., *et al.* (2020). Baseline characteristics and outcomes of COVID-19 patients admitted to a Respiratory Intensive Care Unit (RICU) in Southern Italy. *Multidiscip. Respir. Med*., **15** (1), 704.

ECDC (2021). Data on hospital and ICU admission rates and current occupancy for COVID-19. European Centre for Disease Prevention and Control. https://www.ecdc.europa.eu/en/publications-data/download-data-hospital-and-icu-admission-rates-and-current-occupancy-covid-19 (accessed 28 October 2021).

Eurostat (2019). Overweight and obesity - BMI statistics. https://ec.europa.eu/eurostat/statistics-explained/index.php?title=Overweight_and_obesity_-_BMI_statistics (accessed 29 October 2021).

Grasselli, G., Greco, M., Zanella, A., Albano, G., Antonelli, M., Bellani, G., *et al.* (2020). Risk factors associated with mortality among patients with COVID-19 in intensive care units in Lombardy, Italy. *JAMA Intern. Med.,* **180** (10), 1345–1355.

Grasselli, G., Pesenti, A., Cecconi, M. (2020, March). Critical care utilization for the COVID-19 outbreak in Lombardy, Italy: Early experience and forecast during an emergency response. *Critical Care Med.,* **323** (16), 1545–1546. https://jamanetwork.com. DOI: 10.1001/jama2020.4031

Grasselli, G., Zangrillo, A., Zanella, A. *et al.* (2020). Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to ICUs of the Lombardy Region, Italy. *Critical Care Med.,* **323** (16), 1574–1581. DOI: 10.1001/jama.2020.5394. https://jamanetwork.com

Hajjar, L. A., Costa, I. B. S. da S., Rizk, S. I., Biselli, B., Gomes, B. R., Bittar, C. S., *et al.* (2021). Intensive care management of patients with COVID-19: A practical approach. *Ann. Intensive Care,* **11** (1), 36.

Hong, R., Zhao, H., Wang, Y., Chen, Y., Cai, H., Hu, Y., *et al.* (2020). Clinical characterization and risk factors associated with cytokine release syndrome induced by COVID-19 and chimeric antigen receptor T-cell therapy. *Blood*, **136** (1), 35–36.

Huang, C., Wang, Y., Li, X., Ren, L., Zhao, J., Hu, Y., *et al.* (2020). Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *The Lancet,* **395** (10223), 497–506.

Immovilli, P., Morelli, N., Antonucci, E., Radaelli, G., Barbera, M., Guidetti, D. (2020) COVID-19 mortality and ICU admission: The Italian experience. *Crit. Care,* **24,** 228. DOI: 10.1186/s13054-020-02957-9. https://ccforum.biomedcentral.com/articles/10.1186/s13054-020-02957-9

Lang, C. N., Zotzmann, V., Schmid, B., Berchtold-Herz, M., Utzolino, S., Biever, P., *et al.* (2021). Intensive care resources and 60-day survival of critically-ill COVID-19 patients. *Cureus*, **13** (2), e13210. DOI: 10.7759/cureus.13210.

Langer, T., Brioni, M., Guzzardella, A., Carlesso, E., Cabrini, L., Castelli, G., *et al.* (2021). Prone position in intubated, mechanically ventilated patients with COVID-19: A multi-centric study of more than 1000 patients. *Crit. Care*, **25** (1), 128.

Liu, X., Wang, H., Shi, S., Xiao, J. (2021). Association between IL-6 and severe disease and mortality in COVID-19 disease: A systematic review and meta-analysis. *Postgrad. Med. J.,* 139939. https://pubmed.ncbi.nlm.nih.gov/34083362. DOI: 10.1136/postgradmedj-2021-139939.

Máca, J., Jor, O., Holub, M., Sklienka, P., Burša, F., Burda, M., *et al.* (2017). Past and present ARDS mortality rates: A systematicr. *Respir. Care*, **62** (1), 113–122.

Puah, S. H., Cove, M. E., Phua, J., Kansal, A., Venkatachalam, J., Ho, V. K., *et al.* (2021). Association between lung compliance phenotypes and mortality in COVID-19 patients with acute respiratory distress syndrome. *Ann. Acad. Med. Singapore,* **50** (9), 686–694.

Ranieri, V. M., Rubenfeld, G. D., Thompson, B. T., Ferguson, N. D., Caldwell, E., Fan. E., *et al.* (2012). Acute respiratory distress syndrome: The Berlin Definition. *JAMA,* **307** (23), 2526–2533.

Raymondos, K., Dirks, T., Quintel, M., Molitoris, U., Ahrens, J., Dieck, T., *et al.* (2017). Outcome of acute respiratory distress syndrome in university and non-university hospitals in Germany. *Crit. Care,* **21**, 122.

Sabaka, P., Koščálová, A., Straka, I., Hodosy, J., Lipták, R., Kmotorková, B., *et al.* (2021). Role of interleukin 6 as a predictive factor for a severe course of COVID-19: Retrospective data analysis of patients from a long-term care facility during COVID-19 outbreak. *BMC Infect. Dis.,* **21** (1), 308.

Tonetti, T., Grasselli, G., Rucci, P., Alessandri, F., Dell'Olio, A., Boscolo, A., *et al.* (2021). Synergistic effect of static compliance and D-dimers to predict outcome of patients with COVID-19-ARDS: A prospective multicenter study. *Biomedicines*, **9**, 1228.

Wang, D., Hu, B., Hu, C., Zhu, F., Liu, X., Zhang, J., *et al.* (2019). Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in Wuhan, China. *JAMA*, **323** (11), 1061–1069.

Wei-jie, G., Zheng-yi, N., Yu, H., Wen-hua, L., *et al.* (2020). Clinical characteristics of coronavirus disease 2019 in China. *New Engl. J. Med.,* **382** (18), 1708–1720.

Zanella, A., Florio, G., Antonelli, M., Bellani, G., Berselli, A., Bove, T., *et al.* (2021). Time course of risk factors associated with mortality of 1260 critically ill patients with COVID-19 admitted to 24 Italian intensive care units. *Intensive Care Med.,* **47** (9), 995–1008.

Zhou, F. (2020). Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: A retrospective cohort study. *The Lancet,* **395** (10229), 1054–1062.

Received 15 November 2021
Accepted in the final form 3 July 2022

KLĪNISKIE RAKSTURLIELUMI COVID-19 PACIENTIEM AR INVAZĪVU MĀKSLĪGU PLAUŠU VENTILĀCIJU: NOVĒROJUMU PĀRSKATS PAULA STRADIŅA KLĪNISKĀS UNIVERSITĀTES SLIMNĪCĀ RĪGĀ, LATVIJĀ

Pētījumā izvērtēta slimības gaita, klīniskās pazīmes un to saistība ar iznākumu pacientiem ar smagu Covid-19 norisi, kuriem Intensīvās terapijas nodaļā (ITN) tika nodrošināta invazīva mākslīgā plaušu ventilācija. Pētījums ir retrospektīvs un aprakstošs. Tas norisinājās no 2020. gada 1. oktobra līdz 2021. gada 30. aprīlim Paula Stradiņa Klīniskās universitātes slimnīcas Intensīvās terapijas nodaļā. Pētījumā iekļauti 66 pacienti. No pacientu medicīniskās dokumentācijas tika ievākti demogrāfiskie, klīniskie un laboratoriskie dati, kā arī informācija par mākslīgās plaušu ventilācijas parametriem, uzturēšanās ilgumu ITN un mirstību. 77% no pētījumā iekļautajiem slimniekiem bija vīrieši, mediānais vecums bija 65 gadi. Lielākajai daļai pacientu (67,2%) bija adipozitāte, kā arī vēl vismaz divas blakussaslimšanas, no kurām visbiežākās — kardiovaskulāras slimības (63,6%) un 2. tipa cukura diabēts (38,1%). Mediānais laiks pēc stacionēšanās, līdz tika veikta endotraheāla intubācija, bija astoņas dienas, mediānais ārstēšanas laiks ITN — 12 dienas. Pozicionēšana uz vēdera pielietota vairumā gadījumu (68,2%), nieru aizstājterapija uzsākta trešdaļai pacientu (34,8%). Mirstība ITN sasniedza 86%. Daudzfaktoru analīzē demogrāfiskie dati, laboratoriskie parametri un ārstēšanas taktika netika pierādīti kā būtiski neatkarīgi riska faktori paaugstinātai mirstībai. Tomēr īsāks laiks starp pirmo simptomu parādīšanos un hospitalizāciju ($p < 0{,}001$; HR 0,94), un īsāks laiks starp simptomu parādīšanos un intubāciju ($p < 0{,}001$; HR 0,90) pozitīvi korelē ar labāku klīnisko iznākumu.