ejpmr, 2020,7(12), 480-486

SJIF Impact Factor 6.222

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Research Article

ISSN 2394-3211

EJPMR

MORTALITY AND PREVALENCE OF THROMBOEMBOLISM IN ICU PATIENTS WITH SARS-COV-2, IMPLICATIONS FOR CLINICAL PRACTICE FROM A SINGLE CENTER RETROSPECTIVE OBSERVATIONAL STUDY.

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Article Received on 17/10/2020 **Article Revised on 07/11/2020** **Article Accepted on 27/11/2020**

ABSTRACT

Introduction: in March 2019 Italian ICUs faced an enormous amount of COVID-19 related respiratory failures, we report patients' characteristics, mortality and incidence of thromboembolic events in a single ICU. We investigated whether mortality and thromboembolism were associated with severity scores, respiratory parameters, inflammatory and coagulation markers. **Materials and Methods**: retrospective observational analysis of 56 ICU patients with COVID-19 respiratory failure. Data were retrieved from patients' medical records. **Results**: ICU mortality was 42,8%. Severe hypoxemia was noted on admission with a median pO_2/FiO_2 of 89±34. Higher levels of PEEP at ICU admission (14±4 in non survivors vs 11±2 cmH20 in survivors) and at day 7 (13±5 vs 9±4 cmH20) were associated with higher mortality rate ($p<0.01$). Thromboembolic events were detected in 33,9% of patients. D-Dimer levels were increased at admission and at day 7 (4977±8695 and 3574±5216 respectively), however, no statistically significant association was found between D-Dimer levels and mortality or thromboembolism rate. LMWH prophylaxis < 100U.I/Kg/day resulted in a tendency towards increased mortality. **Conclusions**: COVID-19 showed a high mortality rate in ICU patients. Higher levels of PEEP were associated with worse outcome.Thromboembolism is common and patients require higher dosages of LMWH compared to those commonly used in ICU units for DVT prophylaxis. D-Dimer levels were constantly elevated, but no specific predictor of thromboembolism was identified.

KEYWORDS: ARDS; COVID19; Sars; Pneumonia; Thrombosis; coagulation; Heparin.

1. INTRODUCTION

In 2019 a novel coronavirus (severe acute respiratory syndrome coronavirus 2, SARS-CoV-2) emerged in China and spread globally, causing a global pandemic all over the world.[1][2] Northern Italy experienced a dramatic outbreak of this infection from end of February 2020 causing a massive load for Intensive care units (ICUs) which were overwhelmed with patients with severe pneumonia with extreme hypoxemia often resulting in a severe Acute Respiratory Distress Syndrome according to the Berlin definition.[3][4]

Despite the severe hypoxemia the pathophysiology of this illness seems to be different from conventional ARDS with, at least in the beginning phase of pneumonia, a relatively conserved lung compliance and low recruitability.[5][6] Moreover, coagulation parameters abnormalities have been consistently reported in these patients.[7][8] A study on 81 ICU patients reports an incidence of 25% of venous thromboembolism, suggesting that SARS-CoV-2 may result in vascular involvement with abnormal coagulation and diffuse thrombosis.[9]

A Chinese study showed that 71.4% of non survivors met the International Society on Thrombosis and Hemostasis (ISTH) diagnostic criteria for overt disseminated intravascular coagulation (DIC), compared to 0.6% of survivors.[10]

Several features in Covid-19 patients might contribute to coagulopathy. We analyzed the consecutive patients admitted to our ICU with severe Covid-19 ARDS in order to define the incidence of either venous or arterial thrombosis and to find predictive factors for coagulopathy in these patients.

Assuming that the inflammatory storm caused by Covid-19 pneumonia has been related to a pro-coagulation assessment,[11] we examined the association between the levels of commonly used inflammatory markers (PCR,

Fibrinogen, D-Dimer) and incidence of thrombosis and eventually death.

Hypoxemia has been demonstrated to promote platelet reactivity and to induce expressions of proteins involved in coagulation, thus resulting in thromboembolic events.[12][13] The severity of hypoxemia of Covid-19 patients in ICU during the first 7 days after intubation is remarkable and we studied the eventual impact on both thrombosis and patient outcome.

We also investigated the relationship between doses of prophylactic heparin and both thrombosis and mortality. Low molecular weight heparin (LMWH), as well as unfractionated heparin (UFH), also has an anti-inflammatory activity and this might have an impact on the severity of the illness and thus mortality.[14]

2. MATERIALS AND METHODS

2.1. Study Design and patient selection

This is a retrospective observational analysis of 56 consecutive patients admitted in ICU between February 27th and April 12th2020 with SARS-CoV-2 related pneumonia. The study was approved by local ethical committee (Comitato Etico Provinciale, Brescia, Italy) and all patients were provided with written informed consent to use their outcomes in a report. This study was conducted in an Italian National Health Service Public Hospital (ASST Franciacorta, Chiari, BS).

All patients had SARS-CoV-2 confirmed pneumonia, the diagnosis was based on RT-PCR detection of novel coronavirus nucleic acid in specimens from respiratory tract and chest x-ray positive for bilateral opacities compatible with interstitial pneumonia.

Exclusion criteria were

-Age < 18
-Pregnancy
-ICU stay < 24 hours

All patients received orotracheal intubation and mechanical ventilation and, since they all met the criteria of the Berlin definition for moderate to severe ARDS, targets of mechanical ventilation were tidal volume 6-8 ml/kg, plateau pressure <30 cmH_20 and lowest PEEP based on driving pressure. Prone positioning for 16 consecutive hours/day was used if pO2/FiO2 was below 150 and no contraindications were present (hemodynamic instability, pressure lesions which prevented patients from being pronated).

Although no specific treatment for SARS-CoV-2 pneumonia is available, we treated patients according to a local protocol with lopinavir/ritonavir 400/100 mg twice daily and hydroxychloroquine 200 mg twice daily, all patients received steroids (dexamethasone 20 mg/day for 5 days followed by 10 mg/days for 5 days).

Subcutaneous low molecular weight heparin (LMWH) was used in all patients according to clinical judgement with doses ranging from 4000 U.I. to 6000 U.I.

Data were collected through patients' medical records.

2.2. Outcomes

Primary outcome was ICU mortality in patients with SARS-CoV-2 pneumonia and correlation with thrombosis, hypoxemia, severity scores, inflammatory markers, ICU stay and duration of sedation and curarization.

Secondary outcome was the incidence of thromboembolism and correlation with inflammatory markers, severity scores (Sequential Organ Failure Assessment Score and Sepsis Induce Coagulopathy Score) and hypoxemia.

Thromboembolism was defined as follows

-Pulmonary embolism detected with CT scan or echocardiography.
-Deep venous thrombosis detected with ultrasound.
-Peripheral artery occlusion detected with doppler ultrasound.
-Ischemic stroke detected with CT scan.
-Central venous catheter thrombosis detected with ultrasound.

Baseline data were recorded at admission in ICU (pO2/FiO2, D-Dimer (mcg/l)), Fibrinogen (mg/dl), C-Reactive Protein (CRP (mg/dl)), Platelet count and International normalized ratio (INR) and at 7-10 days from admission.

SOFA and SIC scores were calculated at admission in ICU and at day 7.[15][16]

Ultrasound scanning to assess central venous catheter related thrombosis was performed daily, CT scan for lung and brain thromboembolism and ultrasound for DVT or lung embolism was performed if clinically suspected.

2.3. Statistics

Means or medians and standard deviations were calculated for continuous demographic and outcome data, and after absence of normal distribution was detected by the Kolmogorov-Smirnov test, means or medians were compared by the Mann-Whitney test with $p \leq 0.01$ indicating significant differences. Demographic categorical data are expressed as number of patients. Outcome categorical data are reported as percentages and were compared by Fisher's exact test.

Statistical analysis was performed using Excel (Microsoft, Redmond, WA).

3. RESULTS

56 patients (18 females and 38 males) were admitted between February 27th and April 14th 2020, follow up was completed on May 7th 2020 when the last patient was discharged from ICU. All patients were intubated and mechanically ventilated at ICU admission. All patient presented complete data on their medical records.

All patients received sedatives (propofol and remifentanil iv) and muscle relaxants (atracurium iv). Sedation was titrated to obtain a deep sedation (Richmond Agitation and Sedation Score of -5) and curare was used to maintain muscle paralysis in order to ensure a protective ventilation strategy with tidal volume of 6 ml/kg and maintaining plateau pressure under 30 cmH_20 until the patient was considered ready for weaning from mechanical ventilation. Table 1 summarizes demographical data, ICU length of stay, duration of sedation and curarization.

Table1. Baseline characteristics of patients.

Variable	Median	IQR	Max	Min
Age	66	11	78	38
BMI	28	6	41	20
Days before ICU	3	3,25	12	0
ICU Stay (Days)	10	11	43	2
Curarization(Days)	5	3	15	3
Sedation (Days)	5	3,8	25	3

IQR: Interquartile Range; BMI: Body Mass Index

Oxygenation (pO_2/FiO_2) and Positive End Expiratory Pressure (PEEP) median values as well as SOFA and SIC score are summarized in table 2.

Table2. Oxygenation, PEEP and severity of patients.

Variable	Median	IQR	Max	Min
pO_2/FiO_2 Day 1	89	34	195	42
PEEP (cmH_2O) Day 1	12	4	18	8
pO_2/FiO_2 Day 7	196,5	63	347	69
PEEP (cmH_2O) Day 7	10	4	18	6
SOFA	4	2	10	3
SIC	2	1	4	2

SOFA = Sequential Organ Failure Assessment Score; SIC = Sepsis Induced Coagulopathy Score; IQR = Interquartile Range; PEEP = Positive End-Expiratory Pressure

ICU mortality rate was 42,8% (24/56 patients), table 3 shows demographical data, ICU length of stay, duration of sedation and curarization, oxygenation (pO2/FiO2) and Positive End Expiratory Pressure (PEEP) while inflammatory markers and coagulation parameters in the two groups of patients are summarized in table 4.

Table3. Baseline characteristics of survivors and non survivors.

Variable	Survivors	Non survivors	p
Age	63 (14,25)	68 (6)	0,08
BMI	26,5 (4,25)	29 (6,5)	0,11
Days before ICU	3 (3,5)	3 (3,5)	0,85
ICU Stay (Days)	11,5 (10,25)	7 (5)	0,002
pO_2/FiO_2 Day 1	89,5 (33,5)	87,5 (33,25)	0,39
PEEP (cmH_2O) Day 1	11 (2)	14 (4)	0,004
pO_2/FiO_2 Day 7	167 (101,5)	148,5 (77,5)	0,02
PEEP (cmH_2O) Day 7	9 (4)	13 (5,25)	0,0007
SOFA	4 (1)	4 (2,25)	0,06
SIC	2 (1)	2 (1)	0,40
Curarization (Days)	4 (3)	6 (3,25)	0,003
Sedation (Days)	8 (3,5)	7,5 (6)	0,34
Thrombosis	34,3%	33,3%	0,88

Data are presented as Median and IQR; SOFA = Sequential Organ Failure Assessment Score; SIC = Sepsis Induced Coagulopathy Score; PEEP = Positive End-Expiratory Pressure

Table4. Inflammatory markers and coagulation parameters of survivors and non survivors.

Variable	Alive	Dead	p
CRP Day 1 (mg/dl)	17,7 (17,4)	17,9 (14,8)	0,37
CRP Day 7 (mg/dl)	3,7 (4,8)	12,8 (18,9)	0,10
Fibrinogen Day 1 (mg/dl)	725,5 (332)	737 (233)	0,33
Fibrinogen Day 7 (mg/dl)	593 (192,5)	662,5 (211,2)	0,07
D-Dimer Day 1 (mcg/dl)	4796,5 (4985,75)	7228 (10052)	0,28
D-Dimer Day 7 (mcg/dl)	3543 (5786)	4825 (3506)	0,35
Platelet Day 1 ($x10^3/mm^3$)	242 (129,75)	233 (81,7)	0,39
Platelet Day 7 ($x10^3/mm^3$)	259 (89,5)	194,5 (165,5)	0,08
INR Day 1	1,13 (0,29)	1,17 (0,12)	0,48
INR Day 7	1.01 (0.07)	1,03 (0,05)	0,26

Data are presented as Median and IQR; CRP = C-Reactive Protein; INR = International Normalized Ratio

ICU stay and duration of muscular blockade were significantly longer in patients who did not survive, PEEP was also significantly higher in patients with worse outcome.

Severe hypoxemia was common at admission and improved at day 7 but we did not find statistically significant differences between patients with favorable and unfavorable outcome.

Total thromboembolism rate was 33,9% (19/56 patients) with 4 patients (7,1%) presenting thrombosis of 2 different sites and 1 patient in >2 sites. In most cases (12 patients, 21,40% of all patients) thrombi were found on central venous catheter, in the deep jugular vein, 7 patients (12,50%) had pulmonary thromboembolism, 2 patients (3,50%) had ischemic stroke and in 4 cases (7,10%) thrombosis in other sites.

Two thromboembolic events (one pulmonary embolism and one massive stroke) were fatal and one peripheral artery occlusion required lower limb amputation.

Table 5 shows demographical data, ICU length of stay, duration of sedation and curarization, oxygenation (pO_2/FiO_2), PEEP, SOFA and SIC score while inflammatory markers and coagulation parameters in the two groups of patients are summarized in table 6.

Table 5. Baseline characteristics of patients with and without thrombosis.

Variable	Thrombosis	Non Thrombosis	p
Age	65 (9)	67 (15)	0,82
BMI	27 (4)	28 (7,5)	0,94
Days before ICU	3 (4)	3 (4)	0,34
ICU Stay (Days)	10 (14)	9,5 (5,5)	0,34
pO_2/FiO_2 Day 1	90 (37)	85(39)	0,063
PEEP (cmH_2O) Day 1	12 (4)	12 (4)	0,13
pO_2/FiO_2 Day 7	167,5 (92,8)	155 (57)	0,41
PEEP (cmH_2O) Day 7	9,5 (4)	10 (5)	0,13
SOFA	4 (4)	4 (3)	0,38
SIC	3 (2)	2 (1)	0,3
Curarization (Days)	5 (3)	5 (3,5)	0,46
Sedation (Days)	6 (2)	8 (3,75)	0,04

Data are presented as Median and IQR; SOFA = Sequential Organ Failure Assessment Score; SIC = Sepsis Induced Coagulopathy Score; PEEP = Positive End-Expiratory Pressure

Table 6. Inflammatory markers and coagulation parameters of patients with and without thrombosis.

Variable	Thrombosis	Non Thrombosis	p
CRP Day 1 (mg/dl)	18,7 (12,5)	17,5 (10)	0,33
CRP Day 7 (mg/dl)	3,37 (9,71)	5,4 (14,9)	0,16
Fibrinogen Day 1 (mg/dl)	702 (484)	761 (282,5)	0,1
Fibrinogen Day 7 (mg/dl)	540,5 (258,5)	652 (234)	0,007
D-Dimer Day 1 (mcg/dl)	6817 (11632)	3193 (5191,5)	0,09
D-Dimer Day 7 (mcg/dl)	6661,5 (7886)	3343 (3133)	0,035
Platelet Day 1 ($x10^3/mm^3$)	267 (135)	227 (113)	0,19
Platelet Day 7 ($x10^3/mm^3$)	241,5 (88,5)	244 (170,5)	0,41
INR Day 1	1,22 (0,18)	1,14 (0,26)	0,45
INR Day 7	1,05 (0,06)	1,03 (0,06)	0,28

Data are presented as Median and IQR; CRP = C-Reactive Protein; INR = International Normalized Ratio

Remarkably, no differences were found between the two groups for all variables except for lower levels of fibrinogen at day 7 in patients who developed thrombosis.

All patients received LMWH (subcutaneous enoxaparin 4000 or 6000 U.I. according to clinical judgment) as part of ICU standard practice for DVT prophylaxis. By relating dosage and patients' weight we discovered that only 53,4% of patients received a daily dose of 100 U.I./kg/day which is considered a cut off for optimal prophylactic dosage.[17] LMWH was shifted to higher dosages (100 U.I./kg twice a day) when thromboembolism was detected.

Table 7 shows patient distributions related to LMWH starting dose; mortality and thromboembolism in the two groups are also expressed.

Table 7. Correlation between dosing of LMWH, mortality and incidence of thromboembolic events.

LMWH dose	N	%	Thrombosis incidence	Mortality
<100 U.I./KG	25	44,6	7/25 (28%)	14/25 (56%)
100U.I/KG	31	55,4	12/31 (38,7%)	10/31(32,2%)

N = number of patients

Disseminated Intravascular Coagulation (DIC) score according to ISTH Criteria for Disseminated Intravascular Coagulation (DIC) was calculated retrospectively in all patients based on ICU admission parameters. Only 5 patients reported a score ≥ 5 consistent with overt DIC, however, only 3 of these 5 patients developed clinically evident thrombosis.[18]

4. DISCUSSION

According to our experience, the mortality rate in patients with severe ARDS SARS-CoV-2 related (42.8%) is comparable with findings in severe ARDS as in the LUNG SAFE study in 2016 (46%).[19]

Patients showed severe hypoxemia after intubation in ICU (median pO_2/FiO_2 at day 1 = 89 ± 34), which markedly improved after one week of intensive treatment (median pO_2/FiO_2 at day 7 = 196.5 ± 63).

PEEP levels resulted significantly higher in non survivors and even though these patients were more hypoxemic at day 7, this difference was not statistically significant. This finding is consistent with the evidence that SARS CoV-2 pneumonia seems to have a different pathophysiology from other causes of ARDS; in particular, lung compliance is not greatly reduced (at least in early stages of the disease), therefore high levels of PEEP may not be beneficial or could even be dangerous, since the negative hemodynamic impact of high intrathoracic pressure, which reduces right heart function and tissue perfusion.[20] Furthermore, setting higher PEEP might contribute to Ventilator Induced Lung Injury by overinflating aerated lung units and increasing lung inflammation.[21]

Duration of muscular blockade and ICU stay were significantly increased in patients who did not survive (6 ± 3,25 days compared to 4 ± 3 days and 11,5 ± 10,25 vs 7 ± 5 days respectively), we hypothesize that patients with worse respiratory parameters needed a prolonged protective mechanical ventilation, hence the longer use of muscle relaxants.

Thromboembolism in our patients has been a frequent finding, with more than 30% of patients developing such complication during their ICU stay, however, we assume that the real incidence might be even higher, since subclinical episodes may have not been identified. Our results are consistent with those reported by the Chinese experience.[9]

Incidence of thrombosis in critically ill is enhanced in particular because of malignancy, surgery and trauma. None of our patients had these comorbidities, however the incidence of thromboembolic events in our sample is much higher than the one reported in the general ICU population (33,9% vs 6-10%).[22][23] A paucity of data regarding thromboembolic events in severe ARDS are available, however, in a study on ARDS from H1N1 flu, 37% of patients had thromboembolic events. Coagulation disfunctions seem to play a significant role in the pathogenesis and severity of COVID-19.

We found only one study so far focused on thrombosis of central venous catheters and found an incidence of 24% in ICU patients,[24] which is similar to our results (21,4%).

Dolhnikoff et al. published a study based on minimally invasive autopsies and described fibrinous thrombi in small pulmonary arterioles in areas of both damaged and preserved lung parenchyma as well as in the glomeruli and superficial dermal vessels, suggesting a diffuse activation of the coagulative system.[25]

In our experience, thrombosis was not associated with increased mortality or longer ICU stay but, as stated before, subclinical thromboembolic events could have been missed.

We did not find any significant association between thrombosis and other patient related factors such as age, severity at admission or laboratory markers. Literature is very controversial about the predictive value of D-dimer.[25][26] In our experience D-dimer levels where extremely elevated in all patients, with no statistically significant difference in the group of patients with

thromboembolism compared to the one without it. Tang et al. investigated the incidence of DIC (as diagnosed according to the validated ISTH criteria) in patients with severe coronavirus pneumonia: it was much more frequent in non-survivors (71.4 %) than in survivors (0.6%).[27]

In our population only 5 patients (8.9%) met the diagnostic criteria for overt DIC and only 3 of these patients developed a clinically evident thrombosis. Remarkably in our experience all patients with DIC survived.

A diffuse inflammatory state was present in all patients as reflected by elevated CRP levels on admission, but we did not find a significant positive correlation with CRP levels and mortality or thrombosis incidence.

Fibrinogen levels at day 7 were significantly lower in patients who developed thrombosis; however, fibrinogen levels were higher than 100 mg/dl, which represents one of the criteria for overt DIC.

Patient treated with lower dosages of LMWH showed higher mortality (even if not statistically significant). This is consistent with many other studies: intravascular thrombosis plays a main role in the pathophysiology of COVID-19; thus, a more aggressive treatment with LMWH than the usual ICU regimen should be considered. In literature there is no agreement on recommended doses of thromboprophylaxis agents in ICU patients.[22] Both LMWH and UFH, however, have been demonstrated to downregulate inflammation by inhibiting cytokine gene expression and activation of NF-kB.[28] It is not clear, then, whether increasing the doses of heparin reduces mortality by inhibiting the inflammation chain or because of the anticoagulant role.

5. CONCLUSIONS

SARS CoV-2 related pneumonia is a severe illness which showed a high mortality rate in ICU patients. Despite the severity of hypoxemia, using higher levels of PEEP appears to worsen patients' outcome.

Thromboembolism is a common feature of these patients and requires higher dosages of LMWH compared to those commonly used in ICU units for DVT prophylaxis, we recommend using at least 100 U.I./kg/day in patients without evidence of DVT or other signs of thromboembolism.

Even though we did not find any statistical correlation between thrombosis and biochemical markers, a clear trend towards high values of D-Dimer in patients who developed thromboembolism was noted, D-Dimer monitoring should be recommended to better define which patients may benefit from a more aggressive treatment with LMWH.

In our opinion the high incidence of thromboembolic events should lead to future research on the thrombogenic mechanisms of SARS CoV-2 and to the development of therapeutic strategies eventually including anticoagulants and anti-aggregants.

Limitations

This is a retrospective study on a limited number of patients, LMWH dosage was prescribed according to clinical judgment and not on a specific protocol.

ACKNOWLEDGEMENTS

None

DECLARATION OF INTEREST

None

FUNDINGS SOURCE

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors

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