UDK 37

ISSN 2545 - 4439
ISSN 1857 - 923X

INTERNATIONAL JOURNAL

Institute of Knowledge Management

KNOWLEDGE

KIJ Vol. 45 No. 4 pp. 745 - 928 Skopje 2021

KNOWLEDGE

INTERNATIONAL JOURNAL

SCIENTIFIC PAPERS
VOL. 45.4

April, 2021

INSTITUTE OF KNOWLEDGE MANAGEMENT
SKOPJE

KNOWLEDGE

International Journal Scientific Papers Vol. 45.4

Print: GRAFOPROM – Bitola

Editor: IKM – Skopje

Editor in chief
Robert Dimitrovski, PhD

KNOWLEDGE - International Journal Scientific Papers Vol. 45.4

ISSN 1857-923X (for e-version)
ISSN 2545 – 4439 (for printed version)

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CONTENTS

D-DIMER LEVELS AS A BIOMARKER FOR DISEASE SEVERITY AND MORTALITY IN COVID-19 CRITICALLY ILL PATIENTS

Biljana Lazarova
Clinical Hospital Stip, Republic of N. Macedonia blazarova@yahoo.com
Biljana Eftimova
Clinical Hospital Stip, Republic of N. Macedonia beftimova@yahoo.com
Strahil Gazepov
Clinical Hospital Stip, Republic of N.Macedonia gazepovstrahil@gmail.com
Zorica Naumovska
Faculty of pharmacy-Skopje, Republic of N. Macedonia zose@ff.ukim.edu.mk

Abstract: Purpose As the critically ill patients with COVID-19 pneumonia suffered from high thrombotic risk and the effect of COVID-19 on coagulation is still not well determined, the aim of our study was to evaluate the risk factors associated with mortality in COVID-19 patients and assess the use of D-dimer as a biomarker for disease severity and clinical outcome.

Methodology We conducted a retrospective study of critically ill patients admitted to an intensive care unit (ICU) because of severe COVID-19 pneumonia Fifty five critical COVID-19 patients in the intensive care unit of the Clinical Hospital in Stip-The Republic of North Macedonia in three mounths period December, 2020 - Fevruary, 2021 were enrolled in the study and were divided into survivors and non-survivors. The diagnosis of severe COVID-19 pneumonia was according to World Health Organization (WHO) interim guidance and it was confirmed by RNA detection of the SARS-CoV-2 in clinical laboratory. The demographic and clinical information were collected. Peripheral venous blood sample was taken and routine blood examination with platelet counts and D-dimers was performed on day of admission and at the time of discharged the ICU unit for the survivor group of the patients and the day of death of the non-survivor group. All patients receive appropriate supportive therapies during the hospital stay and tromboprophylaxis with low molecular weight heparin (LMWH, 40-60mg enoxaparin/day) in line with adopted guidelines.

Statistical analysis of the data was performed and appropriate parametric and non-parametric test were conducted. Continuous variables were expressed as median (interquartile range) and compared with the Mann-Whitney U test. A p-value of < 0.05 was considered statistically significant. Stat Graphics centurion 19 was used for statistical analysis.

Results Fifty five patients were enrolled into the study. The mean age was 67 ± 10 years; most of them were male (63.6%). Seventeen patients (31%) survived and 38 patient (69%) have died during the treatment in the ICU in the clinical hospital in Stip. The mean age in the survived group of patients was 66 ± 9 years; most of them were male (76.5%), whereas in the group of non-survivors mean age of patients was 68 ± 10 years with 42.1% women. Our results have suggested that the age does not influents the rate of survival ($p=0.4$). Our results have suggested that the D-dimer values depend on the gender. Our result have confirmed statistically significant higher D-dimer value on the admission in the ICU in female patients ($p=0.05$) and on the leave of ICU unit ($p=0.024$). The present study shows that abnormal coagulation results, especially markedly elevated D-dimer are common in deaths with NCP.

Conclusions Recent clinical experience suggests that severe COVID-19 is commonly complicated with coagulopathy with elevated D-dimer values and severe disease is accompanied with higher D-dimer values in comparison with patients with mild Covid-19 clinical form of disease. In severe cases hypercoagulability is accelerated and disseminated intravascular coagulation is possible clinical outcome. The effect of Coid-19 infection on hemostatic function remains still unknown.

Recommendations Abnormal coagulation results, especially markedly elevated D-dimer may have the potential to guide therapy and prognosis evaluation in criticaly ill patients with confirmed Covid-19 infection.

Keywords: D-dimer levels, biomarkers, Covid 19

1. INTRODUCTION

Coronavirus disease-19 (COVID-19) is the disease caused by 2019-nCoV/SARS-CoV-2, a novel β coronavirus of group 2B (Zhou P et al, 2020). The illness ranges from asymptomatic or mild infection to severe respiratory tract infections in humans such as severe acute respiratory syndrome (SARS). Presentations include fever, coughing, dyspnea, myalgia, prolonged coagulation profiles, and sudden death. Viral acute infections are associated with a procoagulant state, and the resultant hypercoagulability may in severe cases accelerate leading to disseminated intravascular coagulation (DIC) (Chen, 2020; Huang 2020). Approximately one-fifth of the infected individuals

develops severe to critical disease requiring intensive care support a cause of pneumonia. As recent literature data described, severe COVID-19 is commonly complicated with coagulopathy with elevated D-dimer; moreover, a pooled analysis showed that D-dimer values are considerably higher in COVID-19 patients with severe disease than those without (Tang et al, 2020).

Since the emergence in Wuhan, China in December 2019, COVID-19 has increased rapidly in China and progressed worldwide. On January 30, 2020, WHO declared the outbreak as a Public Health Emergency of International Concern (PHEIC). As of May 27, 5,488,825 cases have been confirmed globally, including in Americas, Europe, Eastern Mediterranean, South-East Asia, and Africa, and 349,095 deaths have been reported (Covid-19 situation report 128, 2019). Coagulopathy was reported, and D-dimer elevations were seen in 3.75–68.0% of the COVID-19 patients (Zhou F at al, 2020). Previous studies in community-cquired pneumonia (CAP) and chronic obstructive pulmonary disease (COPD) patients have shown that D-dimer level is higher in severe cases and may be used as a prognostic biomarker (Frouchter et al, 2015), and D-dimer > 1 μg/ml is one of the risk factors for mortality in adult inpatients with COVID-19 (Zhou F at al., 2020). However, the role of D-dimer in COVID-19 patients has not been fully investigated. The aim of on conducted study, we showed D-dimer levels in critically ill patient by imaging staging, in-hospital death was the evaluation of the role of D-dimer as a biomarker for disease severity and clinical outcome critically ill patients admitted in the intensive care unit-ICU.

2. MATERIALS AND METHODS

Retrospective study was conducted of 55 critically ill patients with confirmed pneumonia admitted to an intensive care unit (ICU) of the Clinical Hospital in Stip-The Republic of North Macedonia in three mounts period December 2020 - Fevruary, 2021. Patients enrolled in the study were divided in two groups, survivors and non-survivors.

Confirmed cases were defined as those with epidemiological history, consistent with two clinical manifestations, and microbiological evidence (respiratory or blood specimens positive for SARS-CoV-2 by real-time reverse transcription polymerase chain reaction (RT-PCR) assay according to World Health Organization (WHO) interim guidance. Symptom onset is determined by the earliest clinical manifestations consistent with COVID-19, such as fever, cough, dyspnea, muscle pain, and fatigue, recorded in medical history taken upon admission. We retrospectively collected demographic, clinical data, laboratory parameters, chest CT imaging, and prognosis through electronic patient data and medical records using standardized data collection form.

The diagnosis of severe COVID-19 pneumonia was also according to World Health Organization (WHO) interim guidance and it was confirmed by CT imaging at radiology department. Peripheral venous blood sample was taken and routine blood examination with platelet counts, D-dimers, CRP and LDH was performed on day of admission (T0) and at the discharge day for the patients in a survivor group and the day of death for the patients in a non-survivor group from the ICU unit. All patients receive appropriate supportive therapies during the hospital stay and tromboprophylaxis with low molecular weight heparin (LMWH, 40-60mg enoxaparin/day or unfractionated heparin 25000 IE in continued infusion) in line with adopted guidelines.

Statistical analysis of the data was performed and appropriate parametric and non-parametric test were conducted. Continuous variables were expressed as median (interquartile range) andcompared with the Mann-Whitney U test. A pvalue of < 0.05 was considered statistically significant. Stat Graphics centurion 19 was used for statistical analysis.

3. RESULTS

Critically ill patients hospitalized in ICU unit were confirmed with RT-PCR and transferred from referral center for the novel coronavirus infection. We included 55 consecutive inpatients between December, 2020 and February, 2021 in the final analysis. The mean age of the 55 patients was 67 ± 10 years, ranging from 40 to 86 years. Most of them were male (63.6%). 17 patients (31%) survived and 38 patient (69%) have died during the treatment in the ICU in the clinical hospital in Stip. The mean age in the survived group of patients was 66 ± 9 years; most of them were male (76.5%), whereas in the group of non-survivors mean age of patients was 68 ± 10 years with 42.1% women. (Table 1)

Table 1. Demographic characteristic of critically ill patients hospitalized in ICU unit

Parameters	All patients (n==55)	Survivors (n=17)	Non- survivors (n=38)	P-Value
Age (years)	67±10	66±9	68±10	0.4
Sex (male/female)	35/20	13/4	22/16	

The results have suggested that the age does not influents the rate of survival (p=0.4). Results have suggested that the D-dimer values depend on the gender. Our result have confirmed statistically significant higher D-dimer value on the admission in the ICU in female patients (p=0.05) and on the discharge of ICU unit (p=0.024) as presented in the Table 2.

Table 2. Influence of the gender on D-dimer value at admission an at discharge of ICU

Gender	**n**	**D-dimer value at admission in ICU (ng/ml)**		**P-Value**	**gender**	**n**	**D-dimer value at discharge of ICU (ng/ml)**	
		mean	SD	0.05			mean	SD
male	32	2370.56	2557.37		male	25	4606.4	5897.91
female	20	3545.45	2830.1		female	11	6190.0	4040.2
Total	52	2822.44	2700.44		Total	36	5090.28	5391.1

The platelet counts were at the normal level (150-450 x 10^9L) (262.3±79.4) x 10^9L in the group of survivors and (262.6±88.3) x 10^9L in the group of non-survivors without any statistical significance of the differences. Our results have confirmed that the gender does not influence the platelets counts on the admission of ICU with (p=0.3).Also our results have confirmed that platelet counts on the admission in ICU of the patients did not influence the survival of the Covid -19 patients as presented in Table 3.

Table 3. Influence of the gender on platelets count at admission in ICU and influence of the platelets counts on survival

Gender	**n**	**Platelets count (10^9L) at admission in ICU**		**P-Value**	**Patient**	**n**	**Platelets count(10^9L)at leave of ICU**	
		mean	SD	0.3			mean	SD
male	32	31	240.58		survivor	15	262.6	79.36
female	20	20	259.25		non-survivor	36	241.78	88.41
TTotal	52	51	247.90		Total	51	247.9	85.60

The results of our study have confirmed that the days of hospital stay at intensive unit care did not influence the rate of survival in the group of evaluated sever Covid-19 patients. (Table 4)

Table 4. Influence of the days spent inICU on survival of Covid-19 patients

Patient	**n**	**Days spent in ICU**	
		mean	SD
survivor	17	4.82	3.4
non-survivor	38	5.1	5.16
Total	55	5.02	4.7

4. DISCUSSIONS

We demonstrated that in patients diagnosed with COVID-19, D-dimer elevation upon admission was common and was associated with both increased disease severity and in-hospital mortality. D-dimers are one of the fragments produced when plasmin cleaves fibrin to break down clots. The assays are routinely used as part of a diagnostic algorithm to exclude the diagnosis of thrombosis. However, any pathologic or non-pathologic process that increases fibrin production or breakdown also increases plasma D-dimer levels (Linkins et al, 2017). Examples include deep vein thrombosis/pulmonary embolism, arterial thrombosis, disseminated intravascular coagulation, and conditions such as pregnancy, inflammation, cancer, chronic liver diseases, post trauma and surgery status, and vasculitis. Among critically ill patients admitted to the emergency room, infections, instead of VTE/PE, are the most common reason for D-dimer elevation (Lippi et al, 2014) [9]. In our study, no patient had confirmed PE/DVT, and only three patients in the non-survivor D-dimer group (3/55, 1.6%) with D-dimer levels of 10000 ng/ml, 12000 ng/ml, and 10420 ng/ml had ISTH-DIC scores of ≥ 5, which is laboratory evidence compatible with overt DIC. Thus, the

majority of the included patients with D-dimer elevation in our study did not have overt DIC, so we have lmited information to run into the conclusion that D-dimer elevation is related with DIC.

There is a significant correlation between D-dimer levels and disease severity stratified by the area of affected lungs on chest CT, oxygenation index, as well as clinical staging according to the interim guideline. A higher percentage of D-dimer elevation was confirmed in the reported study than previously reported. This may be due to the higher percentage of severe/critically ill cases referred to ICU, which is another demonstration of the correlation between D-dimer level and disease severity. The obtained results have suggested that the assay may be used early as a marker of severity before chest CT scans or as a complement to CT and clinical staging. As it was confirmed that the in-hospital mortality was associated with increased D-dimer levels, it is evident that this test may be used as a single useful biomarker for clinical outcome in patients with COVID-19.

The findings suggested associations between D-dimer levels and disease severity as well as mortality. There is still lack of evidence for the mechanisms of D-dimer elevation and for determination if the inceased D-dimers level is specific effect of SARS-CoV-2 infection or it is consequences of systemic inflammatory response. In SARS-COV-2 infection, dysregulation of coagulation/anti-coagulation cascades results in worsening lung pathology (Gralinski et al, 2015). In influenza, the pathogenesis by augmenting viral replication and immune pathogenesis can be attributed to an aberrant coagulation system, including both the cellular and protein components (Yang et al, 2016). The pathological features of COVID-19 include diffuse alveolar damage with cellular fibromyxoid exudates, desquamation of pneumocytes and hyaline membrane formation, pulmonary edema with hyaline membrane formation, and interstitial mononuclear inflammatory infiltrates, dominated by lymphocytes, which resemble those seen in SARS and MERS coronavirus infection (Xu et al, 2020; Channappanavar et al, 2017). Presumably, the observed D-dimer elevation signify a hyperfibrinolysis state and increased inflammatory burden induced in SARS-COV-2 infection.

5. CONCLUSIONS

In conclusion, D-dimer levels are commonly elevated in patients infected with SARS-CoV-2. Significantly higher levels are found in patient population with critical illness and may be used as a prognostic marker for in-hospital mortality. Abnormal coagulation results, especially markedly elevated D-dimer may have the potential to guide therapy and prognosis evaluation in criticaly ill patients with confirmed Covid-19 infection.

REFERENCES

Channappanavar, R., & Perlman, S. (2017). Pathogenic human coronavirus infections: causes and consequences of cytokine storm and immunopathology. Semin Immunopathol, 39(5), 529-539.

Chen, N., Zhou, M., Dong, X., Qu, J., Gong, F., Han, Y., Qiu, Y., Wang, J., Liu, Y., Wei, Y, et al. (2020). Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet, 395(10223), 507–13.

Coronavirus disease (COVID-19) Situation Report 128. https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports.

Fruchter, O., Yigla, M., & Kramer, M.R. (2015). D-dimer as a prognostic biomarker for mortality in chronic obstructive pulmonary disease exacerbation. Am J Med Sci., 349(1), 29–35.

Gralinski, L.E., & Baric, R.S. (2015). Molecular pathology of emerging coronavirus infections. J Pathol., 235(2),185-95.

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

Linkins, L.A., & Takach Lapner, S. (2017). Review of D-dimer testing: good, bad, and ugly. Int J Lab Hematol., 39(S1), 98–103.

Lippi, G., Bonfanti, L., Saccenti, C., & Cervellin, G. (2014). Causes of elevated D-dimer in patients admitted to a large urban emergency department. Eur J Intern Med., 25(1), 45–8.

Tang, N., Li, D., Wang, X., & Sun, Z. (2020). Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost., 2020(18), 844–847.

Yang, Y., & Tang, H. (2016). Aberrant coagulation causes a hyper-inflammatory response in severe influenza pneumonia. Cell Mol Immunol.,13(4), 432–42.

Xu, Z., Shi, L., Wang, Y., Zhang, J., Huang, L., Zhang, C., Liu, S., Zhao, P., Liu, H., Zhu, L., et al. (2020). Pathological findings of COVID-19 associated with acute respiratory distress syndrome. Lancet Respir Med., 8(4), 420–2.

Zhou, F., Yu, T., Du, R., Fan, G., Liu, Y., Liu, Z., Xiang, J., Wang, Y., Song, B., Gu, X., et al. (2020). Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet., 395(10229), 1054-62.

Zhou, P., Yang, X., Wang, X., Hu, B., Zhang, L., Zhang, W., Si, H., Zhu, Y., Li, B., Huang, C., et al. (2020). A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature, 579(7798), 270–3.