http:// ijp.mums.ac.ir
Original Article (Pages: 13895-13903)

Coronavirus Disease 2019 in Patients with Thalassemia; Emerging Challenges

Mozhgan Hashemieh[1], *Fariba Shirvani [2]

[1]Pediatric hematologist and oncologist, Imam Hossein Medical Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

[2]Pediatric Infections Research Center. Research Institute for Children Health, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

Abstract

Background

The World Health Organization (WHO) has announced that severe acute respiratory syndrome corona virus-2 (SARS-CoV-2) outbreak is a public health emergency requiring international concern. Thalassemia syndromes are the most prevalent monogenic hemoglobin disorder in world and Iran is located on thalassemia belt, so this type of hemoglobinopathy has a critical importance in our country.

Materials and Methods: In this overview, the research was conducted by screening the relevant articles evaluating the COVID-19 in patients with thalassemia. An electronic search was performed in online data bases of Scopus, Sid.ir, EMBASE, Cochrane, Web of Science and Medline (via PubMed) with English and Persian language from December 2019 up to November 2020.

Results

Overall, 59 articles could be originally identified, 43 of which were excluded and 16 articles have been investigated. Thalassemic patients had a higher risk for severe clinical events due to 2019 novel corona virus. Presence of comorbidities could aggravate the course of COVID-19 in these patients. In thalassemic patients, the protocol of transfusion should not be altered. Also in asymptomatic thalassemic cases, iron chelation should not be stopped but in thalassemic patients with confirmed COVID-19 infection, iron chelation must be discontinued.

Conclusion

According to low number of reported cases of infected thalassemic patient with confirmed COVID-19, there are many unanswered question in management of these vulnerable patients. In this setting treatment decision need to be individualized on a case-by-case basis. In order to deliver an appropriate treatment for these patients, a teamwork between attending clinicians is of utmost importance.

Key Words: COVID-19, SARS-CoV-2, Coronavirus, Thalassemia, Hemoglobinopathy.

*Please cite this article as: Hashemieh M, Shirvani F. Coronavirus Disease 2019 in Patients with Thalassemia; Emerging Challenges. Int J Pediatr 2021; 9(7): 13895-903. DOI:**10.22038/IJP.2020.53675.4254**

Corresponding Author:

Fariba Shirvani, M.D, Address: Imam Hossein Medical Center, Shahid Madani Street, Tehran, Iran.

Email: shirvanifariba@rocketmail.com

Received date: Jul. 12, 2020; Accepted date: Feb.12, 2021

1- INTRODUCTION

Thalassemia syndromes are the most prevalent monogenic disorder in the world that presents as a hereditary hemolytic anemia. The important characteristic of this hemoglobinopathy is defective biosynthesis of α or β chins. Imbalance in α/β globin chain ratio results in ineffective erythropoiesis, chronic hemolytic anemia and iron-overload (1). Patients with transfusion dependent thalassemia (TDT) often present with severe anemia in early infancy or childhood and need lifelong transfusions in order to survive. Non-transfusion dependent thalassemia (NTDT) often manifesting later in childhood or even adulthood and do not need regular transfusions and sometimes on certain situations, transfusion is indicated for them (2). The consequence of these repeated transfusions is iron accumulation in different organs such as heart, liver and pancreas, hence thalassemic patients need iron chelator drugs in order to increase their life span (3).

Complications due to iron overload present much earlier in patients with TDT in comparison to NTDT group (4). Iran is located on thalassemia belt and the gene frequency is approximately 4% (5). WHO has announced that 2019 novel corona virus disease (COVID-19) caused by SARS-CoV-2 is a public health emergency that needs international concern (6). According to WHO recommendation, severity of COVID-19 could be classified as mild, moderate, severe and critical. In mild type, gentle clinical symptoms without pneumonia on chest CT-Sscan. In moderate type, fever and other respiratory symptoms such as cough with pneumonia on chest CT scan and in severe types, respiratory distress (respiratory rate ≥ 30 / min) and hypoxia (oxygen saturation ≤ 93%) exists. In critical type, always respiratory failure requiring mechanical ventilation, shock or other organ failure presents. In this type, patients need intensive care unit (ICU) admission (7). Thalassemia patients are at increased risk for developing of severe complications from the COVID-19. However, the outbreak of SARS-COV-2 has an important effect on patients, their families and physicians (8). This study, reviews the management strategies and provides some important recommendations for patients with thalassemia.

2- MATERIALS AND METHODS

In this review, an electronic search was performed in online databases of Scopus, EMBASE, Sid.ir, Cochrane, Web of Science and Medline (via PubMed) with English and Persian language from December 2019 up to November 2020. The single and combination keywords of: "2019 novel coronavirus" OR "2019-nCoV" OR "COVID-19" AND "Thalassemia" OR "Hemoglobin Disorders" have been selected. The references of all included articles were searched to identify additional studies. The title, abstract and full text of all documents identified using these search criteria were screened by two pediatric subspecialists, a pediatric hematologist and oncologist and a pediatric infectious disease specialist. Then the articles describing thalassemic patients who were infected with COVID 19 selected. Overall, 59 articles could be originally identified, 43 of which were excluded after title, abstract or full text reading, because they did not correlate with COVID 19 in thalassemia.

3- RESULTS

A total number of 16 studies were finally selected. The results of these studies have been classified in 3 groups: factors which are contributing in increased susceptibility of thalassemic patients to COVID-19, blood supply challenges during this pandemic and management of thalassemic patients who are infected with COVID 19.

A: Susceptibility of thalassemic patients to COVID-19:

In thalassemia, multiple factors may increase the risk of SARS-CoV-2 infection and even may be associated with a worse clinical outcome in COVID-19. These patients need to repeated hospitalization or visit healthcare facilities for blood transfusions (9).

1. Hemolysis

Both intravascular and extra vascular hemolysis can occur in thalassemia. Any gradual or prompt decline in hemoglobin concentration may lead to an unfavorable prognosis during COVID-19 infection. Therefore, transfusion of packed cell could improve the outcome of these patients (10).

2. Splenectomy

Splenectomy is another therapeutic modality that is often indicated in older age group. Splenectomy could cause susceptibility to bacterial infections and serious life-threatening sepsis. In splenectomized thalassemic patients who are infected with COVID-19, the risk of secondary overwhelming bacterial infection increases (8). Furthermore, repeated transfusions in thalassemic patients results in alteration in circulating lymphocyte subsets leading to partial immune deficiency. Also splenectomy changes the pattern of cytokine production in patients with thalassemia (11). In a study from Indonesia on 116 β-thalassemia major, researchers have found that splenectomized thalassemia major have increased neutrophil count, but significantly decreased neutrophil phagocytosis (12). Up to now, there is no evidence in favor of splenectomy has been associated with increased risk of COVID-19 infection in comparison to general population (13). Karimi et al. in a study from Iran on 15 thalassemic patients with documented SARS-CoV-2 infection and eight symptomatic β -thalassemia patients without performing the test, have been demonstrated that splenectomy was not significantly associated with the fatal outcome. In this study eighty percent of patients with confirmed COVID-19 have been splenectomized (14).

3. Iron overload

Iron overload is the main factor which is responsible for immune deficiency in β-thalassemia. Iron accumulation in thalassemia is associated with toxic radical formation and progressive tissue damage. Iron has a critical role in cytokine activities such as interferon gamma effectors pathways toward macrophage and also nitric acid formation or immune cell proliferation. Hence, this metal is a key element in host immune surveillance (15). In addition, iron overload leads to decreased antibody-mediated and mitogen-stimulated phagocytosis by monocyte and macrophages. Iron accumulation could affect T-lymphocyte subsets and modification of lymphocyte distribution in various parts of the immune system. Moreover, iron overload results in a significant increase in suppressor T cell ($CD8^+$) numbers and activity and a decline in number, activity and proliferation capacity of helper T cells ($CD4^+$). Iron accumulation could alter the production of cytotoxic T cells and immunoglobulin secretion. Furthermore, iron overload may cause suppression of complement system function (16). Iron overload is the principal etiology of elevated production of reactive oxygen species and free radicals leading to oxidative stress in thalassemia major (13). Also there is no association between iron chelation and vulnerability to SARS-CoV-2 infection. However, it is recommended in symptomatic COVID-19 positive thalassemic patients, iron chelation must be stopped (17).

4. Cardiac and hepatic complications

Various pro-inflammatory mediators which has been associated with COVID-19, could play a significant role in occurrence of heart disease and arrhythmia (13). Shi et al. in a study from Wuhan city in China have been shown that cardiac insult is a prevalent condition among hospitalized patients with COVID-19 and it is associated with a higher mortality risk (18). Therefore, in thalassemic patients with cardiac co- morbidities, a close cardiovascular surveillance during COVID-19 outbreak is recommended (13).

Thalassemic patients with a cardiac T2* < 10 milliseconds, or liver iron concentration (LIC) more than 14mg/gr/dry weight of liver and a serum ferritin level > 2000 mg/ml have an increased risk for cardiac complications. Therefore, monitoring of cardiac function in these patients is advisable (19, 20). Another morbidity in TDT is hepatic iron overload, which may lead to chronic liver disease and cirrhosis. Cirrhosis causes immune dysfunction in these patients (21). Advanced liver disease is one of the most significant risk factors for severe type of COVID-19. However still there are many questions about the association between underlying liver disease and the course of SARS-CoV-2 infection (22).

5. Endocrinopathies

Recently adrenal insufficiency due to iron overload has been considered in thalassemia major. Adrenal insufficiency is an emerging issue in transfusion dependent thalassemia patients that needs appropriate treatment (23, 24). Adrenal hypo-function may render the thalassemic patients to severe infections. These patients require glucocorticoid therapy and steroids have been shown to slow down the clearance of viral RNA (ribonucleic acid) (8). Diabetes mellitus leads to immune dysfunction and impairment in immune responses such as T cell and macrophage activation. Chronic hyperglycemia affects negatively on immune system and therefore increases the risk of morbidity and mortality due to both viral and bacterial infections. Therefore, in patients with diabetes, strict glycemic control and adherence to general preventive measures have been recommended (25).

B: Blood supply challenges

The volume of blood donation during COVID-19 outbreak has been decreased dramatically (26). During the COVID-19 pandemic, a marked reduction in blood donor occurs. On the other hand, the demand for blood or blood products may decrease because elective and non-urgent surgical options are deferred. This may compensate somewhat the reduction of blood supply for thalassemic patients who require chronic transfusion in order to survive (8). However, any decline in hemoglobin concentration in thalassemic patients could affect the general condition of these patients and administration of packed cell would improve the clinical outcome in these individuals (10).

One of the most challenging topics during COVID-19 pandemic is the potential of SARS-CoV-2 transmission via blood and blood products. Up to now, there is no evidence that respiratory viruses such as corona viruses have been transmitted by transfusion; however, the possibility of transmission of SARS-CoV-2 virus via transfusion during the incubation period or from asymptomatic individuals needs further investigation (27). Furthermore, confirmed COVID-19 individuals should be deferred from blood donation for at least 28 days after the resolution of symptoms or completion of treatment (28). After the outbreak of SARS (Severe Acute Respiratory Syndrome) and MERS (Middle East Respiratory Syndrome), in some studies pathogen inactivation / reduction technologies (PRTS) have been studied. Some blood products could be damaged by PRT, therefore a single PRT is not recommended for all blood products

(29, 30). Two principal methods for inactivation of viruses in blood products are heating and solvent / detergent (S/D). Also heating causes denaturation of proteins in blood components, so it can be used only for manufactured plasma products. However, PRT methods are expensive and introduction of these technologies for inactivation of COVID-19 in blood products would not be cost-effective and is not advised (27).

C: Treatment of thalassemic patients during COVID-19 pandemic

1. Transfusion

In thalassemic patients, any drop in hemoglobin concentration could deteriorate clinical condition of them; hence the protocol of transfusion should not be altered (10). In thalassemia intermedia, the use of hydroxyurea during SARS-CoV-2 outbreak may be problematic, because this drug is a cytotoxic agent with possible immune-compromising effects which may be contributing to an unfavorable prognosis for these patients (9).

2. Iron chelation

There is no evidence regarding a relation between iron chelation in thalassemic patients and susceptibility to COVID-19. Hence in asymptomatic thalassemic cases, iron chelation should not be stopped. In thalassemic patients with confirmed COVID-19 infection, iron chelation must be discontinued (17). It has been advised for all of febrile transfusion dependent thalassemic patients to stop iron chelators until the fever has subsided and the etiology of fever has been evaluated. However, in patients with severe cardiac hemosiderosis, stopping iron chelation in fever could be harmful (10).

3. Splenectomy

At present, there is no evidence that splenectomy increases the risk of SARS-CoV-2 infection in thalassemic patients, although splenectomized patients in case of fever, should be assessed for secondary bacterial infection, which may have occurred along with COVID-19. In these situations, broad spectrum antibiotics could be helpful (13).

4. Anti-Coagulation

In thalassemic patients, especially thalassemia intermedia, the risk of thromboembolic events increases. Profound hemostatic alteration has been observed in these patients and multiple factors have been attributed to the hypercoagulable state among thalassemia patients (31). There is currently no evidence about increased risk of thromboembolic event in thalassemic patients with COVID-19. However, regarding that severe SARS-CoV-2 Infection is a predisposing factor for coagulopathy, it has been recommended to administer prophylactic anticoagulation for all patients with severe COVID-19 (32). Many patients with severe SARS-CoV-2 infection manifest with disseminated intravascular coagulation or thrombotic microangiopathies. Coagulopathy in these patients has been associated with increased mortality rate (33).

5. Hematopoietic stem cell transplantation and gene therapy

Hematopoietic stem cell transplantation (HSCT), and gene therapy are two therapeutic modalities which can cure thalassemic patients and is the treatments of choice for these cases. However, these patients need prolonged post-transplant immunosuppression. It is still not understood whether this immunosuppression could increase the risk of COVID-19 in these patients, therefore it has been recommended for stable patients such as thalassemia and sickle cell disease, procedures such as HSCT and gene therapy should be stopped during COVID-19 pandemic until this situation stabilizes (10, 32).

6. Novel therapies

Luspatercept is a new medication which has been approved for treatment of both malignant and non-malignant disorders characterized by ineffective erythropoiesis and severe anemia. The effect of this drug is on pathological human erythropoiesis (34). Luspatercept has a significant role as a potential regulator in erythropoiesis and shows an elevated expression in immature erythroblasts in thalassemic patients (35). Piga et al. in an open- label phase 2 study have reported that this medication could increase hemoglobin level in non-transfusion dependent thalassemia (NTDT) patients and also reduces transfusion burden in TDT patients (36). Also, Cappellini et al. in a randomized double blind placebo- controlled study have shown the efficacy of this drug in TDT (37). Currently there is no evidence that thalassemia patients, who infected with COVID-19, should discontinue luspatercept (32).

7. Care of thalassemic patients

Preventive strategies by health workers, clinicians, transfusion wards, parents of patients and patients themselves are mandatory in order to reduce the number of infected thalassemic cases with COVID-19. Thalassemia patients should strictly avoid contact with individuals who manifest symptoms of COVID-19 such as fever and cough (10). Regarding high hospitalization rate of thalassemic patients, nosocomial transmission is one of the main routes of SARS-CoV-2 dissemination among these patients. However, it is strongly recommended to transfuse these patients in an outpatient setting instead hospitals. Washing hands according to WHO recommendations, using sanitizers, wearing proper masks and social distancing are general preventive measures for these individuals (8). In thalassemic patients with symptoms of cough, fever, fatigue or other symptoms suggestive of SARS-CoV-2 infection, it is required to test COVID-19 PCR (polymerase chain reaction) as soon as possible. If the test is positive or a high suspicion for COVID-19, immediately should be contacted with treating clinician (32). Regarding little clinical experience about infected thalassemic patients with COVID-19, clinician should strictly monitor these cases, because this novel virus could exaggerate hemolytic anemia in thalassemia, and therefore an increase in blood requirement (32). In thalassemia patients with severe comorbidities such as those with suboptimal transfusions or severe iron overload or diabetes, a close collaboration of patient's treating physician with a medical team including cardiologist, infectious disease specialist and endocrinologist has been recommended (8). Also the routine tests such as CBC and serum ferritin should continue as usual during COVID-19 outbreak. In clinically stable patients with low iron load, it is better to postpone annual monitoring tests such as magnetic resonance imaging (MRI T2*), dual energy X-ray absorptiometry (DEXA), ophthalmology exam and audiology tests until the stabilization or end of the pandemic in community (8).

4- DISCUSSION

Patients with hemoglobinopathies such as thalassemia are more vulnerable to COVID-19 and may be at higher risk for developing severe complications of SARS-CoV-2 compared to general population (9). However, whether major thalassemia patients get more severe forms of COVID-19 is a challenging item and there are some conflicts about this topic. Motta et al. in a recent study on 11 patients with thalassemia and COVID-19 in Italy have not found increased severity of COVID-19 in thalassemia patients. In their study, 10 of 11 patients were TDT and only one patient had NTDT. All the patients have associated comorbidities and eight of them have been splenectomized. Perhaps small

number of participants in this study may lead to this result and a larger number of cases need to be collected to define the impact of SARS-CoV-2 virus on outcome of thalassemic patients (38). In a survey by De Sanctis et al. 17 centers from 10 countries, 9499 patients with hemoglobinopathies have been participated. In this study 13 cases, 7 with thalassemia major, 3 with thalassemia intermedia and 3 with sickle cell disease, with documented COVID-19 infection were identified. In 6 patients the course of disease was moderate and in 3 cases was severe. A 30 years old female with thalassemia major has been expired due to critical form of SARS-CoV-2 infection in intensive care unit. These authors have found that 70% of symptomatic cases need hospitalization and co morbidities could aggravate the course of this infection in thalassemia (9).

In another study from Iran which was performed as a multicenter, retrospective and cross sectional survey, a total of 15950 thalassemia major and 2400 thalassemia intermedia have been evaluated. 15 confirmed cases with COVID-19 (12 thalassemia major and 3 thalassemia intermedia) had been identified. However, 8 symptomatic suspected β- thalassemia cases (6 thalassemia major and 2 thalassemia intermedia) of COVID-19 were detected. 17 patients (73.9%) had mild to moderate disease and 6 patients (26.1%) have been expired. More than 60% of all participants had at least one comorbidity and 80% of them were splenectomized. In this study, authors have shown that the mortality rate of COVID-19 among thalassemic patients was much higher compared to general population (14). Also in a COVID-19 webinar which was presented by the European Hematology Association (EHA), 51 patients with TDT and confirmed COVID-19 have been reported. 46 patients presented with mild to moderate symptoms, but 5 patients had been hospitalized and 3 cases died (14). Moreover, a hypothesis has been proposed by Lansiaux that β-thalassemia patients (especially in Sardinia – Italy) may have an immunity against SARS-CoV-2 infection. β chain of hemoglobin is a potential target for this virus and could be absent or diminished in the blood of β-thalassemia patients (hypothesis) (39). To date, no detailed study has been performed about the COVID-19 in thalassemia and our knowledge about the impact of COVID-19 on this hemoglobin disorder is insufficient (10).

5- CONCLUSION

Patients with thalassemia are vulnerable to SARS-CoV-2 infection due to their clinical complication. Presence of comorbidities could aggravate the course of COVID-19 in these patients. Therefore, thalassemic patients should strictly follow the general preventive measures such as social distancing and wearing mask. Few cases of thalassemia and COVID-19 have been reported so far. Certainly more data should be collected in order to better evaluate the impact of SARS-CoV-2 infection on patients with thalassemia.

6- CONFLICT OF INTEREST: None.

7- REFERENCES

1. Taher aT, Weatherall DJ, Cappellini MD. Thalassaemia. Lancet. 2018 Jan 13;391(10116):155-67.

2. Saliba AN, Atoui A, Labban M, Hamade H, Bou-Fakhredin R, Mufarrij A, et al. Thalassemia in the emergency department: special considerations for a rare disease. Ann Hematol. 2020 Sep; 99(9):1967-1977.

3. Azarkeivan A, Hashemieh M, Shirkavand A, Sheibani K. Correlation between Heart, Liver and Pancreas Hemosiderosis Measured by MRI T2* among Thalassemia Major Patients from Iran. Arch Iran Med. 2016 Feb;19(2):96-100.

4. Sleiman J, Tarhini A, Bou-Fakhredin R, Saliba AN, Cappellini MD, Taher AT. Non-Transfusion-Dependent Thalassemia: An Update on Complications and Management. Int J Mol Sci. 2018 Jan 8;19(1):182.

5. Hashemieh M, Timori Naghadeh H, Tabrizi Namini M, Neamatzadeh H, Hadipour Dehshal M. The Iran Thalassemia Prevention Program: Success or Failure? Iran J Ped Hematol Oncol. 2015;5(3):161-6. Epub 2015 Jul 20.

6. Singhal T. A Review of Coronavirus Disease-2019 (COVID-19). Indian J Pediatr. 2020;87(4):281-286.

7. WHO. Clinical management of severe acute respiratory infection when novel coronavirus (nCoV) infection is suspected. 2020; https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratoryinfection-when-novel-coronavirus-(ncov)-infection-is-suspected.

8. Farmakis D, Giakoumis A, Cannon L, Angastiniotis M, Eleftheriou A. COVID-19 and thalassaemia: A position statement of the Thalassaemia International Federation. Eur J Haematol. 2020 Jun 23:10.1111/ejh.13476.

9.de Sanctis V, Canatan D, Corrons JLV, Karimi M, Daar S, Kattamis C, et al. Preliminary Data on COVID-19 in Patients with Hemoglobinopathies: A Multicentre ICET-A Study. Mediterr J Hematol Infect Dis. 2020 Jul 1;12(1): e2020046.

10. Chowdhury SF, Anwar S. Management of Hemoglobin Disorders During the COVID-19 Pandemic. Front Med (Lausanne). 2020 Jun 9; 7:306. doi: 10.3389/fmed.2020.00306.

11. Moshtaghi-Kashanian GR, Gholamhoseinian A, Hoseinimoghadam A, Rajabalian S. Splenectomy changes the pattern of cytokine production in beta-thalassemic patients. Cytokine. 2006 Sep; 35(5-6):253-7. doi: 10.1016/j.cyto.2006.09.003.

12. Sari TT, Gatot D, Akib AA, Bardosono S, Hadinegoro SR, Harahap AR, et al. Immune response of thalassemia major patients in Indonesia with and without splenectomy. Acta Med Indones. 2014 Jul; 46(3):217-25.

13. Karimi M, De Sanctis V. Implications of SARSr-CoV 2 infection in thalassemias: Do patients fall into the "high clinical risk" category? Acta Biomed. 2020 May 11;91(2):50-56.

14. Karimi M, Haghpanah S, Azarkeivan A, Zahedi Z, Zarei T, Akhavan Tavakoli M, et al. Prevalence and mortality in β-thalassaemias due to outbreak of novel coronavirus disease (COVID-19): the nationwide Iranian experience. Br J Haematol. 2020 Aug;190(3): e137-e140. doi: 10.1111/bjh.16911.

15. Weiss G. Iron and immunity: a double-edged sword. Eur J Clin Invest. 2002 Mar;32 Suppl 1:70-8.

16. Walker EM Jr, Walker SM. Effects of iron overload on the immune system. Ann Clin Lab Sci. 2000 Oct;30(4):354-65.

17. Cappellini MD, Eleftheriou P, Piga A, Porter J, Taher A, Telfer P. THE COVID–19 PANDEMIC AND HAEMOGLOBIN DISORDERS. A contribution of Thalassaemia International Federation to its global patients' community.2020; version III (updated):1-15.

18. Shi S, Qin M, Shen B, Cai Y, Liu T, Yang F, et al. Association of Cardiac Injury with Mortality in Hospitalized Patients with COVID-19 in Wuhan, China. JAMA Cardiol. 2020 Jul 1;5(7):802-810.

19. Ngim CF, Lee MY, Othman N, Lim SM, Ng CS, Ramadas A. Prevalence and Risk Factors for Cardiac and Liver Iron Overload in Adults with Thalassemia in Malaysia. Hemoglobin. 2019 Mar;43(2):95-100.

20. Casale M, Meloni A, Filosa A, Cuccia L, Caruso V, Palazzi G, et al. Multiparametric Cardiac Magnetic Resonance Survey in Children with Thalassemia Major: A Multicenter Study. Circ Cardiovasc Imaging. 2015 Aug;8(8): e003230.

21. Albillos A, Lario M, Álvarez-Mon M. Cirrhosis-associated immune dysfunction: distinctive features and clinical relevance. J Hepatol. 2014 Dec;61(6):1385-96.

22. Boettler T, Newsome PN, Mondelli MU, Maticic M, Cordero E, Cornberg M, et al. Careof patients with liver disease during the COVID-19 pandemic: EASL-ESCMID position paper. JHEP Rep. 2020 Jun;2(3):100113.

23. Poggi M, Samperi I, Mattia L, Di Rocco A, Iorio C, Monti S, et al. New Insights and

Methods in the Approach to Thalassemia Major: The Lesson from the Case of Adrenal Insufficiency. Front Mol Biosci. 2020 Jan 29; 6:162. doi: 10.3389/fmolb.2019.00162.

24. Motta I, Mancarella M, Marcon A, Vicenzi M, Cappellini MD. Management of age-associated medical complications in patients with β-thalassemia. Expert Rev Hematol. 2020 Jan;13(1):85-94. 25. Puig-Domingo M, Marazuela M, Giustina A. COVID-19 and endocrine diseases. A statement from the European Society of Endocrinology. Endocrine. 2020 Apr;68(1):2-5.

26. Shander A, Goobie SM, Warner MA, Aapro M, Bisbe E, Perez-Calatayud AA, et al. International Foundation of Patient Blood Management (IFPBM) and Society for the Advancement of Blood Management (SABM) Work Group. Essential Role of Patient Blood Management in a Pandemic: A Call for Action. Anesth Analg. 2020 Jul;131(1):74-85.

27. Hashemieh M. Blood Safety in SARS-CoV-2 Infection, Arch Pediatr Infect Dis. Online ahead of Print; 8(3): e104525.

28. European Centre for Disease Prevention and Control. Rapid Risk Assessment: Outbreak of acute respiratory syndrome associated with a novel coronavirus, Wuhan, China; first update. Stockholm: ECDC; 2020, [cited 2020-2-5]. Available from:

https://www.ecdc.europa.eu/sites/default/files/documents/Riskassessment-pneumonia-Wuhan-China-22-Jan-2020.pdf.

29. Rebulla P. The long and winding road to pathogen reduction of platelets, red blood cells and whole blood. Br J Haematol. 2019 Sep;186(5):655-667. doi: 10.1111/bjh.16093.

30. Seltsam A, Müller TH. Update on the use of pathogen-reduced human plasma and platelet concentrates. Br J Haematol. 2013 Aug;162(4):442-54. doi: 10.1111/bjh.12403.

31. Hashemieh M. Thromboembolic Events in Severe Thalassemia Syndromes. Iranian Journal of Blood and Cancer .2020; 12(2): 41.

32. Taher aT, Bou-Fakhredin R, Kreidieh F, Motta I, De Franceschi L, Cappellini MD. Care of patients with hemoglobin disorders during the COVID-19 pandemic: An overview of recommendations. Am J Hematol. 2020 Aug;95(8): E208-E210.

33. Hashemieh M. Hematologic Parameters of COVID – 19: A Review on Alteration of Hematologic Laboratory Findings. Int J Pediatr 2020; 8(9): 11321-929. doi: 10.22038/ijp.2020.50620.4024

34. Pilo F, Angelucci E. Luspatercept to treat β-thalassemia. Drugs Today (Barc). 2020 Jul;56(7):447-458.

35.Bou-Fakhredin R, Tabbikha R, Daadaa H, Taher AT. Emerging therapies in β-thalassemia: toward a new era in management. Expert Opin Emerg Drugs. 2020 Jun;25(2):113-122.

36. Piga A, Perrotta S, Gamberini MR, Voskaridou E, Melpignano A, Filosa A, et al. Luspatercept improves hemoglobin levels and blood transfusion requirements in a study of patients with β-thalassemia. Blood. 2019 Mar 21;133(12):1279-1289. doi: 10.1182/blood-2018-10-879247. Epub 2019 Jan 7.

37. Cappellini MD, Viprakasit V, Taher aT, Georgiev P, Kuo KHM, Coates T, et al. A Phase 3 Trial of Luspatercept in Patients with Transfusion-Dependent β-Thalassemia. N Engl J Med. 2020 Mar 26;382(13):1219-1231.

38. Motta I, Migone De Amicis M, Pinto VM, Balocco M, Longo F, Bonetti F, et al. SARS-CoV-2 infection in beta thalassemia: Preliminary data from the Italian experience. Am J Hematol. 2020 Aug;95(8): E198-E199. doi: 10.1002/ajh.25840. Epub 2020 May 6.

39. Lansiaux E, Pébaÿ PP, Picard JL, Son-Forget J. COVID-19: beta-thalassemia subjects immunised? Med Hypotheses. 2020 Sep; 142:109827.