Case Report

# Delayed Anticoagulation Proteins Recovery in Severe Thalassemia Diseases Compared to Malignancies in Children after Hematopoietic Stem Cell Transplantation

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Alterations of hemostasis have been observed following hematopoietic stem cell transplantation (HSCT). In thalassemia diseases, the evidences of coagulation stimulation have been observed in patients with thalassemia major with and without splenectomy. The comparison between thalassemia disease before and after HSCT, and malignancy has never been reported. The hemostasis parameters in 8 patients with thalassemia disease and 10 patients with malignancy before, day 0, days 14, days 30, days 60, days 90, and days 180 of HSCT were studied. The median (range) ages in thalassemia, malignancy and normal control groups were 8.5 (2 to 17), 11.0 (2.0 to 19.0) and 10.0 (0 to 16.0) years, respectively (p=0.42). D-dimer level was significantly higher during days 14 to 60 of HSCT in both groups when compared to the normal control group. Protein C and antithrombin activities were significantly lower during HSCT in thalassemia when compared to the malignancy and normal control groups, while, no changes of anticoagulation proteins in malignancy group were observed.

***Keywords***: Stem cell transplantation; Hemostasis; Thalassemia diseases; Malignancy

Received 6 May 2021 | Revised 20 July 2021 | Accepted 21 July 2021

**J Med Assoc Thai 2021;104(8):1370-5**

**Website:** http://www.jmatonline.com

Hematopoietic stem cell transplantation (HSCT) is the treatment for malignancies, such as leukemia, lymphoma and solid tumors, hematologic diseases, such as severe aplastic anemia and thalassemia, and immunologic diseases, such as severe combined immune deficiency and chronic granulomatous disease. Although HSCT has advantages in curing the diseases, there are several complications that required close monitoring and prompt management[1].

Abnormal hemostasis is one of the complications after HSCT, resulting in either bleeding or thromboembolism (TE). The incidence of bleeding has been reported to be as high as 84.3%[2]. The locations of bleeding are the gastrointestinal tract, central nervous system, lungs, genitourinary tract and skin[3]. Patients receiving anticoagulant and having graft versus host disease (GvHD) increase risk of bleeding[4]. On the other hand, the incidence of TE has been reported to be as high as 29%[2]. The reported TE include veno-occlusive disease (VOD) or sinusoidal obstruction syndrome (SOS), venous and arterial TE, microangiopathic hemolytic anemia (MAHA)[5]. Patients with history of venous TE and having GvHD increase risk of TE[4]. Bleeding or TE leads to an increased mortality risks, with the odds ratio of 1.5 to 2 compared to those without complications[2].

The etiologies of abnormal hemostasis relate to high doses of chemotherapy, radiation, immunosuppressive agents, and infections that cause endothelial injury, resulting in increasing tissue factor, von Willebrand factor (vWF), and soluble thrombomodulin. The coagulation stimulations are shown by the increased thrombin antithrombin complex (TAT) and prothrombin fragment (F1+2). In turn, this stimulation consumes anticoagulation proteins, as indicated by decreased protein C (PC), protein S (PS) and antithrombin (AT) activities. After

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**How to cite this article:**

Sirachainan N, Iamsirirak P, Pakakasama S, Hongeng S, Chuansumrit A, Kadegasem P, et al. Delayed Anticoagulation Proteins Recovery in Severe Thalassemia Diseases Compared to Malignancies in Children after Hematopoietic Stem Cell Transplantation. J Med Assoc Thai 2021;104: 1370-5.

doi.org/10.35755/jmedassocthai.2021.08.12904

hemostasis is activated, the fibrinolysis results in elevated D-dimer[6].

The alterations of hemostasis during HSCT were reported by Vannucchi et al. The present study was performed on days 7, 14 and 21 in 15 patients underwent autologous HSCT and 14 patients underwent allogeneic HSCT. It was found that fibrinogen, vWF and factor VIII activity increased, but the activities of PC, factor VII and plasminogen decreased[7]. Lee et al also studied the hemostasis changes between days 0 to 21 of HSCT in patients underwent allogeneic HSCT. It was found that PC and AT activities significantly decreased in moderate and severe VOD patients when compared to those with mild or no VOD[8]. Tamaki et al studied 26 patients, from which 16 patients survived, and 10 patients did not. It was found that the latter group had significantly low levels of PC and AT activities from week 1 through to week 3 after HSCT. From week 1 to 5, thrombomodulin and tissue type plasminogen activator-plasminogen activator inhibitor-I complex levels (tPA-PAI-1 complex) were significantly higher in the former group than in the latter group. Through week 1 to week 13, D-dimer or soluble fibrin monomer levels were significantly higher in the latter group than in the former group[9]. The other study was from Matsumoto T et al which included 39 patients. It was found that TAT, D-dimer, tPA-PAI-1 complex were significantly higher in GvHD group[10]. Most of the studies mentioned above enrolled patients with malignancies such as leukemia, chronic myeloid leukemia and myelodysplatic syndrome. In thalassemia, the coagulation stimulations have been demonstrated, mainly due to the abnormal red blood cell surfaces, platelet, and endothelial activation. After HSCT, thalassemia patients showed increased coagulation stimulation and decreased anticoagulation proteins[11]. But, a study compared hemostatic change between thalassemia disease and malignancy has never been reported. Therefore, the present report aimed to demonstrate the changes in coagulation markers and anticoagulation proteins in severe thalassemia compared to malignancy patients from prior to, day 0, days 14, days 30, days 60, days 90 and days 180 of HSCT. The present study was approved by the Ethics Committee of the Faculty of Medicine (ID 02-54-24).

## Case Report

All consented patients were diagnosed with severe thalassemia diseases and malignancies. The normal controls (NC) were normal children who were healthy and had no history of bleeding or TE. Blood samples were collected from all patients prior to HSCT and on day 0 (day of stem cell infusion), days 14, 30, 60, 90, and 180 after stem cell infusion or HSCT. All the blood specimen was collected in the morning, before transfusion. Laboratory testing included coagulation markers (TAT, F1+2 and D-dimer) and anticoagulation proteins (PC, PS, and AT activities). TAT and F1+2 levels were measured by commercial sandwich enzyme linked immune absorbance (ELISA) (Dade Behring®), and D-dimer (VIDAS®) was measured by enzyme linked fluorescent assay (EIFA). PC and AT activities were measured by chromogenic assay and PS activity was measured by automated coagulation functional assay. The SPSS Statistics, version 17.0 (SPSS Inc., Chicago, IL, USA), specifically independent samples t-test and the Mann-Whitney U test, was used to analyze the differences between patients and NC. During follow up appointments, the Friedman test was used to determine the differences in parameters. The diagnosis of VOD was determined by the criteria of hyperbilirubinemia ≥2 mg/dL, painful hepatomegaly, and weight gain >2% form baseline, before day 20 after HSCT[12]. The severity of VOD was classified into three groups: mild, in which no treatment was required, moderate, in which treatment with diuretic or analgesia was required and lastly severe, in which patients either did not recover within 100 days after HSCT or succumbed to death[13].

Total number of subjects was 58, 18 were patients (10 malignancies, 8 thalassemia diseases) and 40 were NC. The median (range) ages in malignancy, thalassemia and NC groups were 11.0 (2.0 to 19.0), 8.5 (2 to 17) and 10.0 (0 to 16.0) years, respectively, (p=0.42). The female to male ratio in patients and controls was not significantly different, at 1 to 1.5, 1.7 to 1 and 1 to 1.4, respectively, (p=0.55). Types of HSCT and conditioning regimens were described in Table 1. Six patients (75%) in thalassemia group developed fever during HSCT; however, only one patient documented of BK virus infection while 8 patients (80%) in malignancy group developed fever; however, 2 patients documented pneumonia and BK virus infection. GvHD prophylaxis for matched related donor (MRD) was cyclosporine A and methotrexate and matched unrelated donor (MUD) was tacrolimus and methotrexate. Acute GvHD was found in 3 patients in thalassemia group (37.5%) and 3 patients (30%) in malignancy group (Table 1).

D-dimer levels were significantly higher on days 14 and 30 in malignancy group, and days 30 and 60

**Table 1.** Data of 18 patients who underwent hematopoietic stem cell transplantation

| Number | Sex | Age (year) | Diagnosis | Conditioning regimen | Type of HSCT | Complication | | | Transfusion | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | GVHD | VOD | Hemorrhage | PRC (mL/kg) | Platelet (U/kg) |
| 1 | F | 8.8 | E/β thalassemia | Bu/Cy | MRD | No | No | No | 49.5 | 0.2 |
| 2 | F | 9.3 | E/β thalassemia | Flu/Bu/Cy/ATG | MRD | No | No | Skin | 366.3 | 2.1 |
| 3 | F | 2.8 | E/β thalassemia | Bu/Cy | MRD | No | VOD | No | 122.1 | 1.0 |
| 4 | M | 8.4 | E/β thalassemia | Flu/Bu/Cy/ATG | MUD | Skin | VOD | Hemorrhagic cystitis | 101.3 | 0.9 |
| 5 | M | 17.4 | E/β thalassemia | Flu/Bu/ATG | MRD | Skin | No | No | 21.5 | 0.1 |
| 6 | F | 10.9 | E/β thalassemia | Flu/Bu/ATG | MUD | Skin | VOD | Epistaxis/ hemorrhagic cystitis | 84.0 | 0.9 |
| 7 | M | 5.6 | Hb H disease | Bu/Cy | MRD | No | No | Skin | 78.0 | 0.3 |
| 8 | F | 4.4 | E/β thalassemia | Bu/Cy | MRD | No | No | No | 33.5 | 0.4 |
| 9 | F | 12.4 | ANLL | Flu/Bu/ATG | MRD | No | No | Skin | 123.0 | 0.9 |
| 10 | M | 12.5 | Medulloblastoma | Carbo/Eto/Mel | Auto | No | No | No | 15.7 | 0.1 |
| 11 | F | 14.9 | Hodgkin lymphoma | BCNU,Eto/Cy | Auto | No | No | Hemorrhagic cystitis | 9.3 | 0.1 |
| 12 | F | 2.3 | Wilm's tumor | Carbo/Eto/Mel | Auto | No | No | No | 30.9 | 0.5 |
| 13 | F | 20.7 | Non-Hodgkin lymphoma | BCNU/Eto/Cy | Auto | No | No | No | 6.1 | 0.1 |
| 14 | M | 10.2 | Neuroblastoma | Flu/Bu | MRD | Liver | No | Epistaxis/skin | 19.6 | 0.6 |
| 15 | M | 4.6 | ALL | Ara/Cy/TBI | MRD | Skin | No | Epistaxis | 19.2 | 3.6 |
| 16 | M | 15.4 | ANLL | Bu/Clofarabine | MRD | Skin | No | No | 34.8 | 0.2 |
| 17 | M | 4.0 | Neuroblastoma | Car/Eto/Mel | Auto | No | VOD | Gastrointestinal/skin | 212.4 | 2.2 |
| 18 | M | 13.8 | Non-Hodgkin lymphoma | BCNU/Eto/Cy | Auto | No | No | No | 0.0 | 0.1 |

ALL=acute lymphoblastic leukemia; ANLL=acute nonlymphocytic leukemia; GvHD=graft versus host disease; HSCT=hematopoietic stem cell transplantation; MRD=matched related donor; PRC=packed red cell; VOD=veno-occlusive disease

Bu/Cy: busulfan 1.1 mg/kg/day (4 days) and cyclophosphamide 50 mg/kg/day (4 days); Flu/Bu/ATG: fludarabine 30 mg/m$^2$/day (6 days), busulfan 1.1 mg/kg/day (6 days), antithymocyte globulin [Fresenius 10 mg/kg/day (4 days), thymoglobulin 1.5 mg/kg/day (4 days)]; Carbo/Eto/Mel: carboplatin 375 mg/m$^2$/day (4 days), etoposide 300 mg/m$^2$/day (4 days) and melphalan 60 mg/m$^2$/day (3 days); Flu/Bu/Cy/ATG: fludarabine 30 mg/m$^2$/day (6 days), bufulfan 1.1 mg/kg/day (4 days), cyclophosphamide 50 mg/kg/day (4 days); BCNU/Eto/Cy: BCNU 100 mg/m$^2$/day (3 days), etoposide 800 mg/m$^2$/day (3 days) and cyclophosphamide 1.5 g/m$^2$/day (4 days), Bu/Clofarabine: busulfan 130 mg/m$^2$/day (4 days) and clofarabine 375 mg/m$^2$/day (4 days); Ara/Cy/TBI: ara-c 3 g/m$^2$/day (4 days) and cyclophosphamide 45 mg/kg/day (2 days); Flu/Bu: fludarabine 35 mg/m$^2$/day (6 days) and busulfan 130 mg/m$^2$ (4 days); Flu/Cy/ATG: fludarabine 30 mg/m$^2$/day (6 days), cyclophosphamide 60 mg/kg/day (2 days), and Fresenius 10 mg/kg/day (4 days)

in thalassemia group when compared to the level in NC group. When compared between malignancy and thalassemia groups, D-dimer level was significantly higher in thalassemia group on days 60. TAT levels in both groups were not significantly different when compared to the level in NC group. The difference was observed to be higher in malignancy group on days 90 when compared to the thalassemia group. F1+2 levels were not different among the 3 groups (Table 2).

PC levels were significantly lower in thalassemia group on pre-HSCT, day 0, days14, 30, 60, 90, and 180 of HSCT when compared to the NC group. PC level was significantly lower in thalassemia group on days 30 and 90 of HSCT when compared to the malignancy group. PS levels were significantly lower in thalassemia group on pre-HSCT, days 30 and 60 of HSCT when compared to the levels in malignancy group. AT levels were significantly lower in thalassemia group on pre-HSCT, days 14, 30, 60, and 90 of HSCT when compared to the level NC group. AT level was significantly lower in thalassemia group days 30 when compared to the level in malignancy group (Table 2).

All blood transfusion was filtered and irradiated. Most of all platelet transfusion was prepared from apheresis technique. Patients in MRD or MUD HSCT group had significant higher total PRC transfusion until day 180 more than those in autologous HSCT group [57.7 (19.2 to 366.5) versus 12.5 (0 to 212.4) mL/kg, p=0.03]. However, no significant difference in platelet transfusion was demonstrated [0.5 (0.1 to 3.6) versus 0.1 (0.1 to 2.2) U/kg, p=0.109]. Thalassemia patients received higher amount of PRC when compared to the malignancy group [81.0 (21.5 to 366.3) mL/kg versus 19.4 (0 to 212.4), p=0.043]. However, no significant differences of platelet transfusion between the 2 groups [0.2 (90.1 to 2.1) versus 0.4 (0.1 to 3.6), p=0.5].

**Table 2.** Laboratory results of 8 thalassemia patients and 10 malignancy patients

| Parameter | Pre-HSCT; median (range) | | Day 0; median (range) | | Days 14; median (range) | | Days 30; median (range) | | Days 60; median (range) | | Days 90; median (range) | | Days 180; median (range) | | Controls; median (range) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Thalassemia | Malignancy | Thalassemia | Malignancy | Thalassemia | Malignancy | Thalassemia | Malignancy | Thalassemia | Malignancy | Thalassemia | Malignancy | Thalassemia | Malignancy | |
| Platelet counts | 376.5* (118.0 to 874.0) | 150.5 (69.0 to 318.0) | 129 (46.0 to 203.0) | 58.5 (46.0 to 178.0) | 34.5 (5.0 to 313.0) | 52.5 (35.0 to 116.0) | 35.5 (20.0 to 105.0) | 71.3 (16.0 to 271.0) | 71.5 (20.0 to 174.0) | 127.5 (35.0 to 226.0) | 118.5 (12.0 to 249.0) | 161 (19.4 to 202.0) | 193 (22.0 to 252.0) | 179 (104.0 to 213.0) | ND |
| D-dimer (ng/mL) | 522.1 (149.2 to 1,462.1) | 356.3 (169.5 to 4,159.7) | 328.2 (146.6 to 2,307.3) | 328.9 (124.9 to 2,001.0) | 326 (102.9 to 9,038.3) | 750* (147.8 to 3,190.6) | 574.1* (239.2 to 3,036.6) | 594.8* (89.1 to 7,804.6) | 515** (220.2 to 628.8) | 281.1 (107.1 to 506.2) | 384.1 (154.4 to 1,118.8) | 278.9 (145.0 to 1,310.4) | 457.4 (185.4 to 1,324.1) | 291.4 (164.5 to 446.6) | 265.3 (157.5 to 395.8) |
| TAT (mcg/L) | 3.8 (2.8 to 15.3) | 5.2 (2.9 to 62.9) | 4 (2.0 to 15.4) | 3.6 (2.2 to 33.8) | 4.8 (3.3 to 15.4) | 4.5 (2.2 to 43.3) | 4.9 (2.9 to 14.3) | 4.3 (2.9 to 36.6) | 4.3 (2.4 to 14.1) | 4.5 (2.4 to 53.7) | 4.1* (2.2 to 11.9) | 6 (3.0 to 44.7) | 5.3 (2.9 to 18.0) | 4.7 (2.2 to 10.4) | 5.3 (3.7 to 8.0) |
| F1+2 (pmol/L) | 191.5 (116.4 to 8,550.7) | 227 (137.8 to 1,259.0) | 269.9 (104.4 to 11,598.0) | 284.3* (185.0 to 2,518.0) | 440.4 (62.7 to 1,088.4) | 311.6 (123.4 to 43,029.5) | 331.1* (173.8 to 1,259.0) | 308.3 (118.8 to 19,877.4) | 213.5 (130.0 to 1,259.0) | 217.9 (116.8 to 9,978.0) | 193.9 (97.3 to 260.5) | 261.1 (185.1 to 1,766.2) | 155.7 (102.9 to 409.7) | 174.2 (107.1 to 942.7) | 189.5 (134.4 to 345.3) |
| PC activity (%) | 60.5* (32.0 to 86.0) | 85 (49.0 to 144.0) | 76* (59.0 to 86.0) | 92.5 (49.0 to 170.0) | 60* (29.0 to 78.0) | 79 (18.0 to 177.0) | 54.5** (22.0 to 76.0) | 80.5 (65.0 to 184.0) | 60.5* (28.0 to 154.0) | 88 (53.0 to 129.0) | 66** (35.0 to 78.0) | 107 (63.0 to 217.0) | 78.5* (35.0 to 89.0) | 100 (81.0 to 186.0) | 96 (81.0 to 109.5) |
| PS activity (%) | 56* (0.0 to 82.0) | 86 (9.0 to 96.0) | 56 (19.0 to 76.0) | 85 (0.0 to 103.0) | 71 (41.0 to 91.0) | 78 (0.0 to 150.0) | 50* (17.0 to 66.0) | 79 (50.0 to 142.0) | 52.5* (0.0 to 85.0) | 87 (0.0 to 117.0) | 66 (47.0 to 89.0) | 85 (14.0 to 128.0) | 66 (10.0 to 128.0) | 85 (22.0 to 143.0) | 68 (55.5 to 84.0) |
| AT activity (%) | 83.5* (56.0 to 104.0) | 90 (76.0 to 925.0) | 94 (61.0 to 109.0) | 95.5 (15.0 to 139.0) | 79* (67.0 to 91.0) | 87.5 (45.0 to 122.0) | 86** (57.0 to 98.0) | 104.5 (84.0 to 113.0) | 84.5* (54.0 to 104.0) | 92 (79.0 to 103.0) | 84* (68.0 to 112.0) | 88 (30.0 to 164.0) | 93.5 (59.0 to 115.0) | 112 (81.0 to 137.0) | 101 (89.0 to 109.5) |

AT=antithrombin; F1+2=prothrombin fragment; ND=not done; PC=protein C; PS=protein S; TAT=thrombin-antithrombin complex

* Significant difference between thalassemia and malignancy, # Significant difference when compared to the controls

Eleven bleeding episodes, one of which required a PRC transfusion, were shared by 9 individual patients. Four patients were in thalassemia group and 5 patients were in malignancy group. Fifty-five percent of those bleeding episodes occurred on day 0 and days 14 of HSCT. Bleeding manifestations were mucosal bleeding in four patients, petechial hemorrhage in four patients and hemorrhagic cystitis in three patients. Moderate VOD was found in four patients between days 8 to 22 of HSCT (Table 1), 3 patients were in thalassemia group and 1 patient was in malignancy group. Patients with VOD recovered after supportive treatment, no anticoagulant and fibrinolytic agents were required.

Parameters in four patients with VOD and 14 patients without VOD, including TAT, F1+2, D-dimer, PC, PS and AT activities prior to and on the days of HSCT, as well as on days 14, were compared to predict the occurrence of VOD. The parameters which had statistical significance was AT level at pre-HSCT which was significantly lower in VOD group [74.0 (56.0 to 93.0)] when compared to non-VOD group [90.0 (77.0 to 925.0)], p=0.031.

## Discussion

To the authors' knowledge, the present report was the longest prospective study of long-term follow-up of hemostasis changes for 6 months of severe thalassemia diseases and malignancies after HSCT. The 2 groups, before HSCT, had the differences of platelet counts which was higher in thalassemia group and PS which was lower in thalassemia group. In addition, the levels of PC and AT were lower in thalassemia group when compared to the NC. These findings may be explained by the hypercoagulable state in thalassemia diseases, more than that in malignancies, resulted in consumption of anticoagulation proteins as shown in the previous study[11] and the present study.

After HSCT, D-dimer, one of the coagulation markers increased on days 14 and 30 of HSCT in malignancy group while the increment was observed on days 30 and 60 of HSCT in thalassemia group when compared to normal subjects. Another coagulation marker, F1+2 levels were also increase on day 0 and days 30 in malignancy group when compared to normal subjects. The highest levels were on days 14 and 30 of HSCT. These results suggested that the coagulation stimulation was observed during HSCT and gradually decreased after days 60 of HSCT. These findings were similar to the previous studies[10,14,15].

The changes of anticoagulation proteins including

PC, PS, and AT activities were observed. PC activity decreased prior and post HSCT throughout the follow up visit in thalassemia group while PC activity was stable in malignancy group. PS activities in thalassemia group were lower than the levels in malignancy group at prior, days 30 and 60 of HSCT. The AT activities were lower in thalassemia group when compared to the levels in normal subjects until days 90 of HSCT. The lowest level was on days 30 of HSCT, similar to the previous studies[8,10,14,15]. These findings suggested that the consumption of anticoagulation proteins in thalassemia group was demonstrated since the time before HSCT, maximized around days 14 to 30, until days 180 of HSCT. The pathogenesis of coagulation stimulation during HSCT has been reported to relate mainly to the endothelial activation causing elevation of tissue factor[6] which may be higher in thalassemia when compared to the malignancy group.

The incidence of bleeding complication in the present study was 50% which was lower than the previous report of 73.5% in patients underwent autologous HSCT and 84.3%in patients underwent allogeneic HSCT[2]. The incidence of VOD in the present study was 22.2%, which was higher than the previous report at 4.7%[2]. The present finding may be explained by the difference of type of HSCT and conditioning regimens, including the higher percentage of regimens containing Busulfan, a chemotherapeutic agent which increases the risk of VOD[2].The bleeding complication and VOD occurred during 4 and 3 weeks of HSCT respectively. The time period of these complications were similar to the previous report[16].

In the subgroup analysis, AT prior to HSCT was significantly lower in VOD group when compared to non-VOD group. PC level in the present study was not significantly different as reported by a previous study[17]. The statistically insignificant difference in PC levels may be due to the small sample size and the low number of VOD patients compared to other studies[18]. The lower level of AT activities may increase risk of VOD in the present study. Other subgroup analysis had been studied, such as bleeding and GvHD, and no significant difference in any parameters was identified. Thalassemia group had higher number of patients with VOD which may be explained by the differences in conditioning regimens, types of HSCT and levels of anticoagulation proteins when compared to the malignancy group.

In summary, the present report suggested delayed recovery of anticoagulation proteins in thalassemia patients underwent HSCT when compared to patients with malignancy; although, there were limited number of patients in each group. The different in proportion of allogeneic and autologous HSCT between the 2 groups may also affect the results of the present report.

## What is already known on this topic?

Both Thalassemia and HSCT activate hemostasis.

## What this study adds?

Delayed recovery of anticoagulation proteins was demonstrated in thalassemia disease after HSCT when compared to malignancy. These results may add to the risk of developing VOD.


## Acknowledgement

The authors would like to thank all physicians and paramedic personnel involved in taking care of the patients. This work was supported by the Funding from Mahidol University. Nongnuch Sirachainan is a recipient of the Career Development Award from the Faculty of Medicine Ramathibodi Hospital, Mahidol University.


## Ethical approval and consent to participate

The present report was approved by the Ethics Committee of the Faculty of Medicine, Ramathibodi Hospital (ID 02-54-24). All patients and parents gave informed consents.

## Authors' contributions

Sirachainan N designed the study. Iamsirirak P performed the study, Pakakasama S, Hongeng S, Chuansumrit A, and Sirireung S involved in patients' care. Kadegasem P and Tirakanjana A performed laboratory. Sirachainan N wrote the manuscript. All the authors have read and approved the final manuscript.

## Conflicts of interest

The authors declared no conflicts of interest.

## References


1. Copelan EA. Hematopoietic stem-cell transplantation. N Engl J Med 2006;354:1813-26.
2. Pihusch R, Salat C, Schmidt E, Göhring P, Pihusch M, Hiller E, et al. Hemostatic complications in bone marrow transplantation: a retrospective analysis of 447 patients. Transplantation 2002;74:1303-9.
3. Nevo S, Swan V, Enger C, Wojno KJ, Bitton R, Shabooti M, et al. Acute bleeding after bone marrow transplantation (BMT)-incidence and effect on survival. A quantitative analysis in 1,402 patients.

Blood 1998;91:1469-77.
4. Gerber DE, Segal JB, Levy MY, Kane J, Jones RJ, Streiff MB. The incidence of and risk factors for venous thromboembolism (VTE) and bleeding among 1514 patients undergoing hematopoietic stem cell transplantation: implications for VTE prevention. Blood 2008;112:504-10.
5. Tsakiris DA, Tichelli A. Thrombotic complications after haematopoietic stem cell transplantation: early and late effects. Best Pract Res Clin Haematol 2009;22:137-45.
6. Bunte MC, Patnaik MM, Pritzker MR, Burns LJ. Pulmonary veno-occlusive disease following hematopoietic stem cell transplantation: a rare model of endothelial dysfunction. Bone Marrow Transplant 2008;41:677-86.
7. Vannucchi AM, Rafanelli D, Longo G, Bosi A, Guidi S, Saccardi R, et al. Early hemostatic alterations following bone marrow transplantation: a prospective study. Haematologica 1994;79:519-25.
8. Lee JH, Lee KH, Kim S, Lee JS, Kim WK, Park CJ, et al. Relevance of proteins C and S, antithrombin III, von Willebrand factor, and factor VIII for the development of hepatic veno-occlusive disease in patients undergoing allogeneic bone marrow transplantation: a prospective study. Bone Marrow Transplant 1998;22:883-8.
9. Tamaki S, Wada H, Ohfuzi K, Shibata T, Masuya M, Kageyama S, et al. Hemostatic abnormalities following bone marrow transplantation. Clin Appl Thromb Hemost 2002;8:125-32.
10. Matsumoto T, Wada H, Nishiyama H, Hirano T, Sakakura M, Nishii K, et al. Hemostatic abnormalities and changes following bone marrow transplantation. Clin Appl Thromb Hemost 2004;10:341-50.
11. Sirachainan N, Thongsad J, Pakakasama S, Hongeng S, Chuansumrit A, Kadegasem P, et al. Normalized coagulation markers and anticoagulation proteins in children with severe β-thalassemia disease after stem cell transplantation. Thromb Res 2012;129:765-70.
12. McDonald GB, Hinds MS, Fisher LD, Schoch HG, Wolford JL, Banaji M, et al. Veno-occlusive disease of the liver and multiorgan failure after bone marrow transplantation: a cohort study of 355 patients. Ann Intern Med 1993;118:255-67.
13. Bearman SI. The syndrome of hepatic veno-occlusive disease after marrow transplantation. Blood 1995;85:3005-20.
14. Brown SA, Davies SV, Fegan C, West R, Giddings J, Whittaker J, et al. Haemostatic and fibrinolytic responses to bone marrow transplantation. Br J Haematol 1999;104:468-74.
15. Yenicesu I, Uçkan D, Cetin M, Tuncer AM, Tezcan I, Gürgey A. Evaluation of coagulation in pediatric bone marrow transplantation patients. Pediatr Transplant 2001;5:430-3.
16. Park YD, Yasui M, Yoshimoto T, Chayama K, Shimono T, Okamura T, et al. Changes in hemostatic parameters in hepatic veno-occlusive disease following bone marrow transplantation. Bone Marrow Transplant 1997;19:915-20.
17. Jevtic D, Zecevic Z, Veljkovic D, Dopsaj V, Radojicic Z, Elezovic I. Veno-occlusive disease in pediatric patients after hematopoietic stem cell transplantation: relevance of activated coagulation and fibrinolysis markers and natural anticoagulants. J Pediatr Hematol Oncol 2011;33:227-34.
18. Faioni EM, Krachmalnicoff A, Bearman SI, Federici AB, Decarli A, Gianni AM, et al. Naturally occurring anticoagulants and bone marrow transplantation: plasma protein C predicts the development of venocclusive disease of the liver. Blood 1993;81:3458-62.