Original Article

Chimerism analysis in hematopoietic stem cell transplantation: Relationship between informativeness of STR profiles and clinical manifestations

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Abstract

Objective: The study was aimed to assess the relationship between short tandem repeat (STR) chimerism analysis and clinical manifestations of hematopoietic cell transplantation (HCT). The practical informative STR loci were evaluated for number, marker, mixed chimerism pattern, post transplanted day and recipient-derived percentage in Thai post-HCT patients.

Method: The retrospective cohort included STR chimerism analytical results of 149 post-HCT patients with malignant and non-malignant hematological diseases at Department of Forensic Medicine, Faculty of Medicine Siriraj hospital during 2012-2018. Data was collected pre-HCT/ post-HCT recipient's and donor's STR profiles, type of diseases, recipient-donor relationship, post-transplanted day and clinical manifestations.

Result: The mixed chimerism (MC) related to the major group such as GVHD, relapse, rejected and cytopenia in both malignant and non-malignant diseases. The practical informative loci were higher correlation to major I group and anemia than theoretical informative loci ($P<0.001$). Average number of practical informative loci was 4 from 10 theoretical loci. Detection limits were 4.98% in bone marrow and 6.06% in peripheral blood. The first MC detection represented at day 16 in malignant and day 21 in non-malignant. The chimerism workup period was optimized at 2 weeks to 3 months. The sensitivity and specificity of STR chimerism test were 88.61% and 81.43%.

Conclusion: This study proved that informative STR profiles associated with major clinical manifestations.

Key words: Chimerism analysis, Hematopoietic cell transplantation, Informative STR loci, Clinical manifestation

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Introduction

The hematological diseases are the common disease which have suffered Thai people and consumed lots of medical personnel, physician time and financial resources. The hematopoietic cell transplantation (HCT) has been used to treat patients with partial response and non-response to conventional therapies. The allogenic stem cell and bone marrow have been widely used as graft for HCT after HLA matching of recipient and donor. However, the serious complications especially graft versus host disease (GVHD), transplant rejection and disease relapse have usually found in many post-HCT patients.[1]

The short tandem repeats (STR) are the regions of human DNA that have been used for forensic personal investigation. The STR amplification by polymerase chain reaction (STR-PCR) has been applied to chimerism analysis for detection of the recipient/donor proportion in post-HCT patients, that substitutes conventional cytogenetic and fluorescence in situ hybridization. The STR chimerism analysis are preferred to use as the diagnostic test and follow-up test for the reason of the predictive power of prognosis and mortality rate.[2, 3] Currently, STR-PCR has become most widely used in chimerism testing owing to diagnostic value of high sensitivity and specificity.[4, 5]

The accuracy of STR chimerism analysis depended on detection limit of methods, laboratory proficiency and clinical correlations. The clinical manifestations were reported by physicians and considered necessary to STR chimerism interpretation. The effective chimerism analysis could particularly predicted survival rate and probability of relapse. The delayed diagnosis of graft rejection and remission could initiate poor prognosis and life threatening. This encourages the new applications in chimerism testing such as Quantitative PCR (qPCR) and Next-generation sequencing (NGS) platforms. Even though, the qPCR-based chimerism analysis was increasing sensitive detection of recipient derived, both qPCR and NGS are non-significantly effective than STR for routine chimerism monitoring.[6 - 8]

The serious post-HCT complications such as GVHD, remission and graft rejection were strongly related to recipient mixed chimerism (MC) but there was not enough information about less severity complications for example anemia, neutropenia, thrombocytopenia, fever and infection. Therefore, the systematical analysis of STR-PCR chimerism tests and the clinical correlation was in a hope to confirm the accuracy of chimerism interpretation. The objectives of this study were to compare clinical characteristics and informativeness of STR chimerism analysis in Thai post-HCT patients.

Methods

This retrospective cohort study included the post-HCT patients with malignant and non-malignant hematologic diseases who received hematopoietic stem cell transplantation (HSCT) and bone marrow transplantation (BMT). All patients had the complete work up for Chimerism analysis by STR-PCR at Serological laboratory, Department of Forensic Medicine, Faculty of Medicine Siriraj hospital between January 2012 to December 2018 (n = 149). All subjects have collected pre-transplant information e.g. genotype of recipient and donor, relationship profile, previous cell supplement therapy and transplanted type. The specimens were peripheral blood samples (n = 864) and bone marrow blood samples (n = 96) which collected from 96 post-HSCT patients and 53 post-BMT patients, that was 120 related and 29 unrelated recipient-donor type. Chimerism testing were done 1-61 times (mean = 6.44) at 9-6,433 days (median = 311) after transplantation. The routine STR-PCR was used AmpFLSTR IdentiFiler Plus® Amplification Kit (Applied Bio-systems, Foster City, CA, USA) and amplified 28-29 cycles on GeneAmp® 9700 thermal cycler (Applied Bio-systems). PCR products

were analysed by capillary electrophoresis with ABI 3500 Genetic Analyzer (Applied Bio-systems) and Genemapper® ID-X software v1.3 (Applied Bio-systems). The IdentiFiler Plus® PCR Amplification Kit included 15 STR loci as D3S1358, *vWA, FGA*, D8S1179, D21S11, D18S51, D5S818, D13S317, D7S820, *TH01, TPOX, CSF1PO,* D19S433, D2S1338, D16S539 and *amelogenin gene* gender determination. The detection limits of commercial STR-PCR was excluded artificial mixture at quantitative level 0.5%. The informative STR profile of 149 donor-recipient pairs were evaluated by classifying chimerism pattern in three types as Type I (only alleles not shared), Type II (one shared and one unshared alleles) and Type III (all alleles were shared) and calculating recipient-derived proportion according to the proposal of Nollet et al.[9] The chimerism pattern Type I 1-5 and Type II 1-2 were defined as theoretical informativeness according to Han et al.[10] The theoretical informative STR loci were markers that had different alleles of donor-recipient matching and probably used to chimerism analysis. The practical informative loci were actually useful markers that have been applied for MC detection in practice. The percentage of recipient-derived in chimerism results were calculated from peak high of alleles in all STR loci which had MC pattern, Coefficient of Variation (CV) was calculated in all MC results.[7] This study compared the post-HCT STR profiles and recipient chimerism percentage with the clinical characteristics e.g. disease, age, donor-relation type, post-HCT day, and medical symptom. The clinical manifestations were reported in laboratory request form by physician, that distinguished to three groups by severity of symptom as Major I group (serious complications: GVHD, graft rejected, disease relapse), Major II group (hematopoietic system involves: anemia, neutropenia, thrombocytopenia, pancytopenia), and Minor group (non-specific immune system involves: fever and serious infection such as pneumonia, urinary tract infection, septicemia). The statistical analyses were preformed using descriptive statistics, cross-tabulation, Chi-square test and Fisher's exact test.

This study was approved by the institutional review board at Faculty of Medicine Siriraj hospital (COA no. Si 198/2018).

Results

All 149 patients were 85 males and 64 females with malignant disease 55% (n = 82) and non-malignant disease 45% (n = 67). The common diseases were acute lymphoblastic leukemia (ALL) (n = 22), acute myeloblastic leukemia (AML) (n = 37), severe aplastic anemia (SAA) (n = 23) and β-Thalassemia (n = 39) (Table 1). The chimerism results were 454 complete chimerism (CC) and 506 mixed chimerism (MC) with 4.99-100% of recipient-derived percentage (mean = 25.11%). Result showed that 83 patients occurred MC at least once, 28 patients MC in the first chimerism test and 66 patients had been persisting CC. The MC was found in malignant group 39.8% (n = 33) and non-malignant group 60.2% (n = 50) when the CC was 74.2% malignant (n = 49) and 25.8% non-malignant (n = 17).

Table 1 Characteristics of 149 patients in gender, disease and donor-recipient relation type

	Variable	CC (n=66)	MC (n=83)	Total (n=149)	P-value
Gender					0.377
	Female	31 (53.0)	33 (39.8)	64 (43.0)	
	Male	35 (47.0)	50 (60.2)	85 (57.0)	
Age					0.009
	Minimum	2	1	1	
	Maximum	59	64	64	
	Mean	31.18	23.07	26.61	
	Median	34	16	28	
	SD	19.62	17.64	19.15	
Disease					0.051
	ALL	16 (24.2)	6 (7.2)	22 (14.8)	
	AML	18 (27.3)	19 (22.9)	37 (24.8)	
	CLL	6 (9.1)	3 (3.6)	9 (6.0)	
	Lymphoma	3 (4.5)	1 (1.2)	4 (2.7)	
	Myelofibrosis	5 (7.6)	3 (3.6)	8 (5.4)	
	Neuroblastoma	1 (1.5)	1 (1.2)	2 (1.3)	
	β-Thalassemia	9 (13.6)	30 (36.1)	39 (36.2)	
	SAA	7 (10.6)	16 (19.3)	23 (15.4)	
	SCID	1 (1.5)	4 (4.8)	5 (3.4)	
Donor type					0.631
	Related	52 (70.8)	68 (81.9)	120 (80.5)	
	Unrelated	14 (21.2)	15 (18.1)	29 (19.5)	

CC = Complete Chimerism, MC = Mixed Chimerism, ALL = Acute Lymphoblastic Leukemia, AML = Acute Myeloblastic Leukemia, CML = Chronic Myeloblastic Leukemia, SAA = Severe Aplastic Anemia, SCID = Severe Combined Immunodeficiency Disease

The practical informative STR loci were observed at median of 4 (0 - 13), the theoretical informative STR loci were 10 (5 - 15) in MC group and 10 (6 - 15) in CC group. The MC patterns (n = 847) were Type I-1 14.28% (n = 121), Type I-2 4.48% (n = 38), Type I-3 4.48% (n = 38), Type I-4 2.12% (n = 18), Type I-5 47.10% (n = 399), Type II-1 12.27% (n = 104), and Type II-2 15.23% (n = 129). The common theoretical informative loci in MC were D13S317 (80.7%), *FGA* (79.5%), *CSF1PO* (77.1%), D2S1338 (73.5%), D21S11 (73.5%) when the practical informative loci were D13S317 (59.8%), *CSF1PO* (58.2%), D7S820 (58.1%), *TPOX* (57.9%) and *vWA* (56.0%) (Table 2).

Table 2 (A) Theoretical and practical informative STR loci in mixed chimerism

Locus	Type I-1	Type I-2	Type I-3	Type I-4	Type I-5	Type II-1	Type II-2	Type III	Theoretical informative[a]	Practical informative[b]
(A) mixed chimerism (n=1,245)										
D8S1179	12	1	1	0	29	9	5	26	68.67	53.77
D21S11	15	3	3	1	30	5	4	22	73.49	54.46
D7S820	5	2	4	2	25	8	8	29	65.06	58.06
CSF1PO	1	0	2	2	31	11	17	19	77.11	58.18
D3S1358	4	1	7	1	20	7	13	30	63.86	55.20
TH01	5	6	3	2	21	6	11	29	65.06	54.00
D13S317	7	6	3	4	30	7	10	16	80.72	59.82
D16S539	5	2	2	0	27	7	4	36	56.63	49.47
D2S1338	11	2	3	1	30	5	9	22	73.49	55.45
D19S433	14	2	1	1	29	3	7	26	68.67	52.78
vWA	8	2	1	0	30	6	9	27	67.47	56.00
TPOX	0	1	0	3	10	11	19	39	53.01	57.89
D18S51	14	2	1	1	25	4	4	32	61.45	52.58
D5S818	11	2	4	0	26	8	4	28	66.27	53.40
FGA	9	6	3	0	36	7	5	17	79.52	55.93
Total	**121**	**38**	**38**	**18**	**399**	**104**	**129**	**398**	**68.03**	**55.14**

[a] Type I + Type II (%), b MC detection in practice (%)

Table 2 (B) Theoretical and practical informative STR loci in complete chimerism

Locus	Type I-1	Type I-2	Type I-3	Type I-4	Type I-5	Type II-1	Type II-2	Type III	Theoretical informative[a]	Practical informative[b]
(B) complete chimerism (n=990)										
D8S1179	11	3	1	0	29	4	1	17	74.24	
D21S11	8	2	1	2	29	3	6	15	77.27	
D7S820	4	1	3	1	19	7	4	27	59.09	
CSF1PO	2	0	2	0	25	9	8	20	69.69	
D3S1358	4	3	1	1	17	9	8	23	65.15	
TH01	5	2	1	0	16	10	12	20	69.69	
D13S317	7	1	3	1	22	6	5	21	68.18	
D16S539	7	1	0	1	23	10	6	18	72.73	
D2S1338	10	1	4	2	28	1	3	17	74.24	
D19S433	5	0	1	0	28	5	12	15	77.27	
vWA	4	2	5	2	19	6	6	22	66.67	
TPOX	1	0	0	1	7	9	14	34	48.48	
D18S51	13	2	2	0	22	4	3	20	69.69	
D5S818	4	4	2	0	25	6	7	18	72.73	
FGA	7	0	4	1	30	8	2	14	78.79	
Total	**92**	**22**	**30**	**12**	**339**	**97**	**97**	**301**	**69.59**	

[a] Type I + Type II (%), b MC detection in practice (%)

The fastest recipient-derived detection was occurred in MC at day 16 in malignant disease (Myelofibrosis) and at day 21 in non-malignant disease (β-Thalassemia) after transplant (median = 84). The serious complication was first reported at day 20 in ALL (GVHD) and at day 75 in β-Thalassemia (GVHD) (median = 38). The longest continuous recipient free duration was day 4,903 in CC and the longest survival MC with chronic GVHD was 6,433 days (Figure. 1).

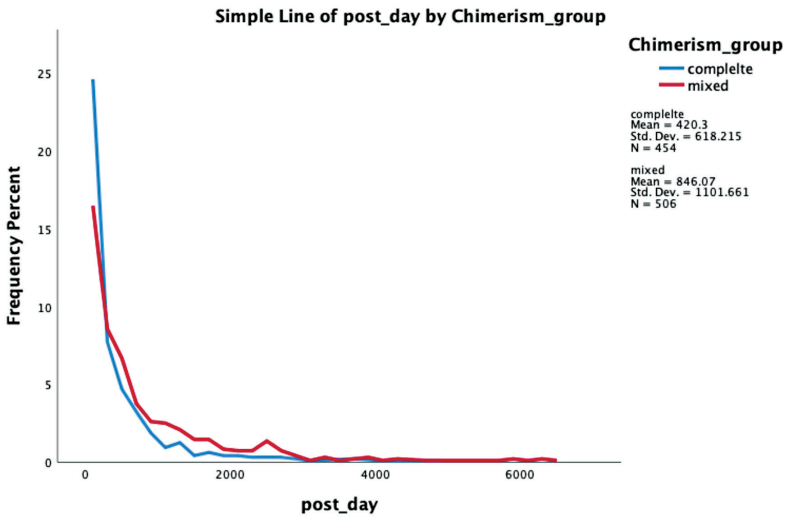

Figure 1 Post-transplanted day in both chimerism groups

The average recipient-derived percentage was 35.96% (4.98 - 100) by peak high cut-off at 10%, imbalance cut-off at 20% and all CV was < 25%. The practical lowest recipient-derived detections were 4.98% (bone marrow blood) in malignant group and 6.06% (peripheral blood) in non-malignant group. The patients were separated by principal clinical manifestation into GVHD (11.6%), relapse (0.8%), graft rejection (2.2%), pancytopenia (7%), anemia (31.5%), neutropenia (0.4%), thrombocytopenia (3%), fever (0.3%), infection (2.1%) and stable (41.1%) by respectively. There were 17 patients with serious complications (graft rejected, GVHD, relapse) that have detected MC at least once in individual chimerism tests with 4.98 - 100% (mean 26.49) of recipient-derived. The practical informative loci were significantly relative to clinical manifestations more than theoretical informative loci in major group including GVHD, relapse, rejection and anemia (Table 3). The MC was correlated to major group (P<0.001) but the minor group was not statically significant (P=0.152). This study showed sensitivity and specificity of STR chimerism analysis in post-HCT patients were 88.61% and 81.43% (Table 4). Nevertheless, the sensitivity and specificity of each STR chimerism testing were 70.71% and 50.37% (major I group) and less than in minor group (21.74% and 46.53%) (Table 5).

Table 3 Comparison of theoretical and practical informative loci according to clinical manifestations

Clinical manifestation	Theoretical loci	Practical loci	P-value	
			Theoretical	Practical
Stable (n=70)	10.84	1.40		
GVHD (n=5)	11.40	4.00	0.630	0.015
Rejected (n=9)	9.67	9.00	0.174	<0.001
Relapse (n=3)	8.33	8.00	0.090	<0.001
Anemia (n=29)	10.76	3.38	0.879	<0.001
Pancytopenia (n=20)	9.05	2.40	0.005	0.104
Neutropenia (n=1)	10.00	1.00	0.734	0.851
Thrombocytopenia (n=5)	9.20	0.80	0.148	0.531
Fever (n=1)	12.00	12.00	0.641	<0.001
Infection (n=6)	10.83	0.00	0.993	0.109
Total (n=149)	**10.43**	**2.59**		

Table 4 Sensitivity and Specificity of STR chimerism analyses (number of patients)

Clinical group	CC	MC	Total	Sens.	Spec.	P-value
Stable	**57**	**13**	**70**			
(A) major I	**0**	**17**	**17**	**100%**	**50.00%**	**<0.001**
GVHD	0	5	5	100%	45.83%	
Rejected	0	9	9	100%	47.14%	
Relapse	0	3	3	100%	45.21%	
(B) major II	**5**	**50**	**55**	**90.91%**	**64.89%**	**<0.001**
Anemia	5	24	29	82.76%	50.83%	
Pancytopenia	0	20	20	100%	51.16%	
Neutropenia	0	1	1	100%	44.59%	
Thrombocytopenia	0	5	5	100%	45.83%	
(C) minor	**4**	**3**	**7**	**42.86%**	**43.66%**	**0.152**
Fever	1	0	1	0.00%	43.92%	
Infection	3	3	6	50.00%	44.06%	
Total	**66**	**83**	**149**	**88.61%**	**81.43%**	

Table 5 Cross-tabulation of STR chimerism analyses and clinical groups (number of tests)

Clinical group	CC	MC	Total	Sens.	Spec.	PPV	NPV
Stable	**265**	**130**	**395**				
A) major I	**41**	**99**	**140**	**70.71%**	**50.37%**	**19.57%**	**90.97%**
GVHD	36	75	111	67.57%	49.23%	14.82%	92.07%
Rejected	3	18	21	85.71%	48.03%	3.56%	99.34%
Relapse	2	6	8	75.00%	47.48%	1.19%	99.56%
(B) major II	**130**	**272**	**402**	**67.66%**	**58.06%**	**53.75%**	**71.37%**
Anemia	66	236	302	78.15%	58.97%	46.64%	85.46%
Pancytopenia	39	28	67	41.79%	46.47%	5.53%	91.41%
Neutropenia	3	1	4	25.00%	47.18%	0.20%	99.34%
Thrombocytopenia	22	7	29	24.14%	46.40%	1.38%	95.15%
(C) minor	**18**	**5**	**23**	**21.74%**	**46.53%**	**0.99%**	**96.04%**
Fever	2	1	3	33.33%	47.23%	0.20%	99.56%
Infection	16	4	20	20.00%	46.60%	0.79%	96.48%
Total	**454**	**506**	**960**	**66.55%**	**67.09%**	**74.31%**	**58.37%**

Discussion

This study informed the correlation of STR chimerism test and clinical manifestations in post-HCT patients as shown in Table 3. The MC detection and practical informative STR loci were correlated to major group: graft rejection, disease relapse, GVHD and anemia resemble to Borrill et al.[11] The STR detection limit was slightly lower in bone marrow blood (4.98%) than peripheral blood (6.06%) that were no significant difference, agreeable to Mousavi et al.[12]

The sensitivity and specificity of STR chimerism analysis were acceptable as shown in Table 4. The sensitivity and specificity of each STR chimerism test were lower than the new technique by q-PCR (Willasch et al.,[13] Lea et al.,[14] Bach et al.[15]) and haplotype counting (Debeljak et al.6) by the reason of lower detection limit, number of informative loci and nature of diseases. The most appropriate period after transplantation for chimerism check-up test was to start at day 15-90 because the first MC detection was at day 16 and median at day 84 while the major clinical manifestation was first reported at day 38 (20-75), that reasonable to Lee et al.,[16] Bader et al.,[17] Miura et al.[18] and Mossallam et al.[19] The long term MC in malignant and non-malignant diseases were found as late as more than 1 year with major group, which consistent to Stikvoort et al.[20] and Levrat et al.[21] This obtained result could be explained by mild chronic GVHD and possibility of response to the adjunctive treatment such as cell replacement, donor lymphocyte infusion and adjuvant chemotherapy.

The MC in malignant and non-malignant diseases were not correlated to minor group, that explained by non-specific symptoms which were usually spontaneously presenting in many hematological patients. The population genetic statistic of Thai post-HCT patients differed from other nationality and this study used the different commercial STR kit, therefore the result of the theoretical and practical informative loci were divergence to Thiede et al.[22] and Han et al.[10] The useful practical informative loci were D13S317, *CSF1PO*, D7S820, *TPOX* and *vWA*, that included in commercial STR kits according to 13 CODIS core STR loci e.g. IdentiFiler®, PowerPlex®, GlobalFiler™.

Conclusion

The study demonstrated that STR chimerism analysis was useful for post-HCT work up test with acceptable sensitivity and specificity. The practical informative loci were significantly correlate to graft rejection, disease relapse, GVHD and anemia. The theoretical informative loci were not correlate to both major and minor clinical manifestations. The most proper time after HCT for first STR chimerism test was at day 15-90. The frequency and duration of follow up testing should be correlated with clinical presentations. The informativeness STR loci of Thai post-HCT patients differ to the other nationality. However, the commercial STR kits are effectiveness for chimerism analysis.

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บทคัดย่อ

การศึกษาผลตรวจติดตามผู้ป่วยโรคเลือดภายหลังปลูกถ่ายเซลล์ต้นกำเนิดเพื่อหาความสัมพันธ์ระหว่าง รูปแบบ ตำแหน่ง ความถี่ และสัดส่วนของสารพันธุกรรม กับอาการทางคลินิก

สุรเชษฎ์ วงศ์วิทยาพาณิชย์

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วัตถุประสงค์: เพื่อศึกษาความสัมพันธ์ระหว่างผลตรวจวิเคราะห์สารพันธุกรรม short tandem repeat (STR) กับอาการทางคลินิกของผู้ป่วยโรคเลือดภายหลังได้รับการปลูกถ่ายเซลล์ต้นกำเนิด เกี่ยวกับ รูปแบบ ตำแหน่ง ความถี่ ระยะเวลา และสัดส่วนของผู้ให้/ผู้รับ

วิธีการศึกษา: ใช้วิธีศึกษาจากเหตุไปหาผลแบบย้อนหลังในผู้ป่วยโรคเลือดทั้งชนิดร้ายแรงและชนิดไม่ร้ายแรง ภายหลังได้รับการปลูกถ่ายเซลล์ต้นกำเนิด ซึ่งได้รับการตรวจ STR chimerism analysis จำนวน 149 ราย โดยวิเคราะห์ข้อมูล ผลตรวจสารพันธุกรรมของผู้ป่วยและผู้บริจาค ชนิดโรค ความสัมพันธ์เครือญาติ ระยะเวลาหลังปลูกถ่ายฯ และอาการทางคลินิก

ผลการศึกษา: พบความสัมพันธ์ระหว่าง mixed chimerism กับอาการทางคลินิกที่สำคัญชนิด GVHD โรคกำเริบ ปฏิกิริยาต่อต้าน และภาวะเซลล์เลือดต่ำ ทั้งในโรคร้ายแรงและไม่ร้ายแรง, พบว่าตำแหน่งของสารพันธุกรรมที่แสดงข้อมูลที่ใช้งานได้จริง (จำนวนเฉลี่ย = 4) สัมพันธ์กับอาการทางคลินิกมากกว่าตำแหน่งบนสารพันธุกรรมที่แสดงข้อมูลในเชิงทฤษฎี (จำนวนเฉลี่ย = 10) ($P<0.001$), พบปริมาณสัดส่วนของผู้รับ/ผู้ให้ที่ตรวจพบได้ต่ำสุดจาก ไขกระดูกเท่ากับ 4.98% และจากเลือดเท่ากับ 6.06% ซึ่งเริ่มตรวจพบหลังปลูกถ่ายฯตั้งแต่วันที่ 16 ในโรคร้ายแรง และวันที่ 21 ในโรคไม่ร้ายแรง ช่วงระยะเวลาเหมาะสมเพื่อส่งตรวจคือ 2 สัปดาห์ ถึง 3 เดือน โดยมีความไว 88.61% และความจำเพาะ 81.43%

สรุปผลการศึกษา: พบว่า มีความสัมพันธ์ระหว่างผลตรวจ STR chimerism analysis ตำแหน่งของสารพันธุกรรมที่แสดงข้อมูลกับอาการทางคลินิกที่สำคัญ

คำสำคัญ: การตรวจติดตามหลังการปลูกถ่ายเซลล์ต้นกำเนิดเม็ดเลือด, การปลูกถ่ายเซลล์ต้นกำเนิดเม็ดเลือด, ตำแหน่งของสารพันธุกรรมที่แสดงข้อมูล, ลักษณะอาการทางคลินิก