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The Necessity of Clinical Rh Phenotypic Serological Detection and Homotypic Infusion in Patients with Repeated Blood Transfusion

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Background: This study analyzed the distribution of Rh serological phenotype in people living in Hangzhou, China, and assessed the necessity of its routine clinical detection and homotypic infusion.

Material/Methods: Blood donors and patients who might need blood transfusion were enrolled into the study, and ABO and 5 major Rh serological antigens (C, c, D, E, and e) were routinely detected. The consistent ABO and Rh serological phenotype blood was transfused between the blood donors and recipients. Irregular antibodies were screened and identified in patients before the blood transfusion. Then, the transfusion adverse effects were monitored and compared with the previous data in the hospital.

Results: The phenotypic frequencies of Rh blood groups were D>C>E>c>e. The CCDee was the most common phenotype and CcdEe was the least common. The detection rate of unexpected antibodies gradually increased, while the unexpected antibodies slowly decreased in the Rh system. There was a correlation between the isotypic infusion of 5 Rh antigens and the detection rate of antibodies in the Rh system (R=0.845). The adverse effects of blood transfusion declined from 19.95% in 2011 with just homotypic ABO infusion to 3.098% in 2019 with the transfusion of homotypic ABO and the 5 major Rh serological antigens.

Conclusions: The consistency of the transfusion with ABO and 5 significant Rh serological antigens could prevent and decrease the high frequency production of isoantibodies, which is of vital importance in reducing the incidence rate of adverse effects in patients receiving transfusions.

MeSH Keywords: Blood Transfusion • Erythrocyte Transfusion • Immunization, Passive • Rh-Hr Blood-Group System

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Background

In 1939, Levine and Stetson discovered the human Rh blood group system, and their study has proven that this system is one of the most critical blood group systems next to the ABO system in clinical importance [1,2]. After 2 of the Rh gene cDNAs were cloned in 1990 [2,3], the study of the genetic structure of the Rh blood group system rapidly progressed.

As one of the most polymorphic systems of the human blood, the Rh blood group system consists of more than 50 antigens [4,5]. However, only 5 antigens are particularly important in clinical practice, and the antigenicity from strong to weak is as follows: D>E>C>c>e [5,6]. If the Rh antigen-antibody system does not match between the blood donor and the receptor, this might cause a hemolytic transfusion reaction, newborns hemolytic disease (HDN), and autoimmune hemolytic anemia [7,8]. At present, the essential antigens D are commonly detected in every hospital of China and in the world, but only a few have detected the other 4 significant antigens, which might be the most crucial cause of immunoreaction.

Our department started to detect the Rh serological phenotype in patients who might need 2 or more blood transfusions, developed the component blood infusion of the same ABO and 5 major antigens of Rh phenotypes since 2013, and generalized the detection to all patients who might need blood transfusion since 2015. The results revealed that the rate from a high level was D, e, C, c, and E, which was in accordance with the reports of previous studies in other populations [9].

After the component blood infusion of consistent ABO and the 5 major Rh antigen types, the adverse effects of blood transfusion in our hospital decreased year by year, from 19.95% in 2012 to 3.098% in 2019, and considerably lowered the occurrence rate. Furthermore, the detection rate of unexpected antibodies gradually increased from 0.18% in 2014 to 0.56% in 2019, while the detection rate of unexpected antibodies slowly decreased in the Rh system in antibody-positive patients, from 72.41% in 2014 to 39.76% in 2019. All these results prove the great importance of Rh homotypic infusion in clinical practice.

Material and Methods

Samples

Approximately 77 180 donor blood samples were supplied by the Blood Center from 2011 to June 2019, and donors who donated 2 times or more were counted as 1 donation using the Blood Center ID numbers. Patients who might need a blood transfusion and applied for it were enrolled in the study. We enrolled 90 891 patients from 2011 to June 2019 in the present study. The total number of samples was 168 071. Adverse effects of patients who received blood transfusions were analyzed in this period at the hospital.

Instruments and reagents

For the indirect anti-globulin assay, micro-column gel cards were purchased from Diana Company. The Rh blood group system appraisal instruments and reagents were obtained from Changchun Company. Spectrum cells (a set of 16) were obtained from Shanghai Blood Biological Medicine Company. Other instruments included the incubation (Diana Company) and centrifugation (BASO Company) process.

Methods

The Rh serological phenotypes of the main 5 antigens in all donors and receptors were detected according to manufacturer's protocols. The irregular antibody specificity of positive samples with the 1 ball micro-column gel method was further identified using the brine and people indirect anti-globulin methods. Patients who received at least 2 blood transfusions were regarded as the same subject using their unique hospital ID number when analyzing the infusion adverse reactions. The same donors and receptors were taken once when analyzing the Rh serological phenotype with the Blood Center ID number. All results were independently checked by 2 staff.

Statistical analysis

All data are presented as mean±standard deviation (SD), and Student's unpaired or paired *t*-test was performed, as appropriate, to compare differences between groups. The Mann-Whitney *U*-test was performed to compare the non-parametric data between the 2 study groups. A *P*-value <0.05 was considered statistically significant. The data were analyzed using GraphPad Prism 5 software (Graph Pad Software, Inc., San Diego, CA, USA).

Results

The distribution of Rh phenotypes in subjects

The blood in our hospital was routinely donated by the Blood Center of Zhejiang Province, and this is the only department entitled to provide blood for the hospital. From January 2011 to June 2019, a total of 77 180 blood products were sent to the hospital. There were 90 891 inpatients who might need transfusions. Repetitions were eliminated using the Blood Center ID numbers on the blood bags for donors and the hospital ID number for inpatients. All 168 071 subjects were detected for both the ABO and 5 major Rh serological antigens.

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Table 1. The serological phenotypes of the 5 major antigens in the Rh blood type of all subjects.

No.	Rh phenotype	Frequency	Percentage (%)
1	CDe/CDe	75541	44.944
2	CDE/cDe	57170	34.014
3	CDe/cDe	14587	8.679
4	cDE/cDE	11973	7.123
5	cDE/cDe	5610	3.338
6	CDE/CDe	1317	0.784
7	cDe/cDe	576	0.343
8	cde/cde	506	0.301
9	CDE/cDE	357	0.212
10	Cde/cde	304	0.181
11	Cde/Cde	56	0.033
12	cdE/cde	38	0.023
13	CDE/CDE	16	0.010
14	CdE/cde	18	0.011
15	CdE/Cde	2	0.001

Among these subjects, a total of 15 phenotypes were detected. Among these, CCDee was the highest in frequency (44.944%), followed by CcDEe (34.014%), CcDee (8.679%), ccDEE (7.123%), and ccDEe (3.338%). The detailed information is summarized in Table 1. The serological antigen "D" negative was written as "d".

The antigen distribution of the Rh blood group system in donors

For all donors, the ratio of these 4 ABO types was as follows: A 30.530%, B 28.478%, O 32.244%, and AB 8.748%. For patients, the ratio was as follows: A 31.417%, B 25.632%, O 34.563%, and AB 8.32%. These results are consistent with those in previous studies [10,11]. There were almost twice as many male donors as female donors. Type "O" was the most common type in Rh (D) positive and negative phenotypes among males and females. The type, along with the other 4 major Rh antigens, was detected in 77 180 donors. Among these donors, 76 636 (99.295%) donors were RhD, and 544 (0.705%) donors were Rhd. In terms of the type of RhD, the CCDee phenotype was the most common type, while in Rhd, this was ccdee. The results are presented in Table 2.

Table 2. The distribution of the Rh blood group system antigen detection in donors.

RH	ABO								Total
	A	A	B	B	O	O	AB	AB	
	Male	Female	Male	Female	Male	Female	Male	Female	
CCDee	7032	3547	6537	3459	7452	3721	2082	1082	**34912**
CcDEe	5090	2885	4767	2586	5759	2606	1355	809	**25857**
CcDee	1379	723	1236	604	1466	637	352	189	**6586**
ccDEE	1188	492	1078	510	1241	601	293	164	**5567**
ccDEe	524	237	464	324	562	286	157	102	**2656**
CCDEe	108	49	101	46	130	68	33	29	**564**
ccDee	57	26	60	21	63	30	20	9	**286**
CcDEE	32	19	36	26	47	20	8	11	**199**
ccdee	59	41	37	31	63	36	20	17	**304**
Ccdee	25	27	23	16	42	30	8	7	**178**
CCdee	9	5	2	6	3	2	2	1	**30**
ccdEe	1	0	3	1	7	7	0	0	**19**
CcdEe	3	1	1	2	0	3	1	1	**12**
CCDEE	3	1	1	1	1	2	0	0	**9**
CCdEe	0	0	0	0	0	1	0	0	**1**
Total	**15510**	**8053**	**14346**	**7633**	**16836**	**8050**	**4331**	**2421**	**77180**

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Table 3. The antigen distribution of the Rh blood group system in patients.

RH	ABO								Total
	A	A	B	B	O	O	AB	AB	
	Male	Female	Male	Female	Male	Female	Male	Female	
CCDee	7155	5622	5741	4523	7952	6222	1931	1483	**40629**
CcDEe	5481	4332	4464	3657	6098	4607	1468	1206	**31313**
CcDee	1399	1134	1149	933	1542	1206	362	276	**8001**
ccDEE	1191	843	937	721	1238	961	304	211	**6406**
ccDEe	493	390	448	335	603	428	141	116	**2954**
CCDEe	154	94	108	83	148	101	33	32	**753**
ccDee	51	36	43	39	62	42	8	9	**290**
CcDEE	28	22	26	12	35	24	5	6	**158**
ccdee	30	38	22	20	38	38	6	10	**202**
Ccdee	16	24	14	10	25	24	6	7	**126**
CCdee	9	4	2	1	5	3	1	1	**26**
ccdEe	4	1	3	2	3	4	1	1	**19**
CCDEE	2	0	1	2	0	2	0	0	**7**
CcdEe	1	0	1	0	3	1	0	0	**6**
CCdEe	1	0	0	0	0	0	0	0	**1**
Total	**16015**	**12540**	**12959**	**10338**	**17752**	**13663**	**4266**	**3358**	**90891**

Antigen detection of the Rh blood group system in patients

For patients, the ratio of the 4 ABO types was almost the same as that of donors, but the percentage for females was much higher than that for donors. Type "O" continued to be the most common type among patients in our hospital. The RhD type, along with other major Rh antigens, was detected in 90 891 patients. Among these patients, 90 511 (99.582%) patients were RhD and 380 (0.418%) patients were Rhd. For the type of RhD, the CCDee type was the major type, while for Rhd, the major type was ccdee, and this was consistent with that of the blood donors. The results are presented in Table 3.

The adverse reaction of transfusion from 2011 to Jun 2019

In China, every hospital must comply with the principles of homotypic ABO and RhD infusion for patients who need routine blood transfusions, which is the same for our hospital since before 2013. The investigators started to detect the 5 major antigens of the Rh serological phenotype in patients who might need blood transfusions at least 2 times or more. Then, the component blood infusion was prepared with the same ABO and Rh serological phenotype since October 2013, and the detection was generalized for all patients who needed blood transfusions since October 2014. The total number of infusions for patients from 2011 to June 2019 was 3108, 3329, 4283, 4585, 4871, 4885, 4092, 4373, and 2444, respectively. The number of adverse effects of blood transfusion was 62, 58, 37, 36, 18, 17, 12, 13, and 8, respectively. The adverse effects of blood transfusion in our hospital have decreased year by year: 19.95%, 17.42%, 8.69%, 7.85%, 3.69%, 3.49%, 3.016%, 3.126%, and 3.098%. This proves the delicate relationship between the homotypic Rh transfusion and the adverse effects of blood transfusion. The results are presented in Figure 1. The study investigated the type of adverse effects involving transfusion of different Rh phenotype, and the results are shown in Supplementary Table 1.

We also assessed the rates of adverse effects among patients who received homotypic infusion and the patients who did not receive homotypic infusion from 2015 to Jun 2019 (as before October 2014 we did not detect all the patients' Rh serological phenotype). The results showed that there is a statistically significant difference between the 2 groups (P <0.05) (Supplementary Table 2).

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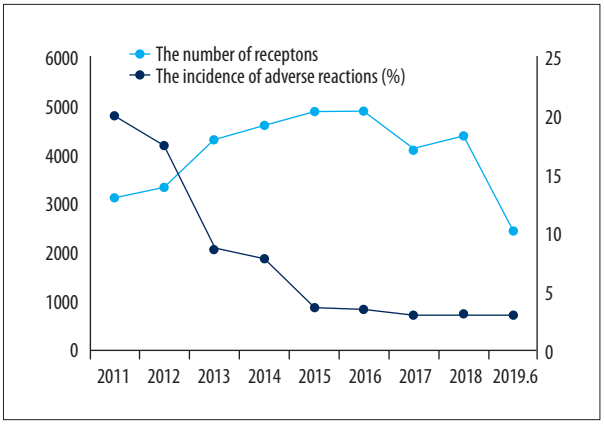

Figure 1. The number of receptors and adverse incidences from 2011 to June 2009: With the increase in the number of receptors year by year, the adverse incidence rate decreased from 19.95% to 3.098% after the same Rh serological phenotype infusion, which remained very stable each year. The "2019.6" refers to the period from January to June 2019.

Distribution of the 5 major Rh antigens

In the present study, the distribution of the 4 major Rh antigens in Rh (D) positive and negative subjects was analyzed. Interestingly, the most significant difference was the percentage of C and c: C was much higher than c in RhD, while c was much higher than C in Rhd. There was no EE in Rhd in the present study. Furthermore, the present study analyzed the antigen frequency (AF) of the 5 major Rh antigens (Table 4). It was noteworthy that AF is an extremely important clinical indicator for predicting the common alloantibodies that could be formed in patients after receiving repeated transfusions, thereby contributing to the selection of antigen-negative blood for patients with alloantibodies [12]. This is in accordance with studies on multi-transfused thalassemias and hemodialysis patients published from a center in north India [13,14].

The correlation among the 5 major antigens of Rh blood transfusions with different antibodies detection

Since our department started to detect the Rh serological phenotype of patients who might need blood transfusion in 2013, the accordance of Rh infusion was stable after 2015, since Rh 5 major antigens were detected in all patients. The rates of the Rh 5 major antigens, in accordance with the transfusion (accordance of Rh) from 2013 to June 2019, were 67.3%, 73.7%, 90.1%, 89.7%, 90.0%, 92.8%, and 92.3%, respectively. The results of the irregular antibody detection revealed that the positive rate gradually increased (0.15%, 0.18%, 0.16%, 0.26%, 0.38%, 0.54%, and 0.56%, respectively), while the Rh system antibody-positive rate decreased (59.13%, 72.41%, 55.56%, 55.56%, 47.14%, 40.90%, and 39.76%, respectively). In addition, a negative correlation was observed between the accordance of the Rh and positive rate of Rh antibody detection (P=0.0167, r=0.9747). In the further analysis of the Rh system antibody, it was found that the E antibody-positive rate was very high: 59.53%, 58.62%, 48.14%, 42.28%, 41.43%, 32.73%, and 31.89%, respectively. There was also a correction between the accordance of the Rh and the positive rate of E antibody detection (P=0.0833, r=0.9000). All these results are presented in Figures 2 and 3. In the study, we analysis the antibody-positive patients according to the body system, and found that the proportion of circulatory system and digestive system was relatively higher than in the other 6 systems, and the difference was statistically different ($p<0.05$) (Supplementary Table 3).

Discussion

The Rh blood group is generally recognized as the second most crucial system in transfusion medicine after the ABO blood type [1,2]. The present study statistically analyzed the distribution difference of the Rh serological phenotype in the population of Hangzhou, Zhejiang province, to determine the necessity of its clinical routine detection and homotypic infusion. We enrolled 168 071 subjects, and the ABO and 5 major Rh serological antigens were detected. Then, the adverse effects of blood transfusions from 2011 to June 2019 in our hospital were compared. The results reveal that this has a large effect in lowering the adverse effects after the same Rh phenotype infusion.

The antigen frequency of RhD-positive subjects in the present study was 99.450%, while the frequencies of the other Rh antigens were C 88.872%, c 54.226%, E 45.517%, and e 92.654%. This was in line with previous studies [9,15]. Although antigen D is the most potent immunogen, the AF of the other 4

Table 4. The antigen frequency (AF) of other Rh antigens (C, c, E, and e) in Rh (D) positive and negative objects in the study.

Number of objects	C AF (%)	c AF (%)	E AF (%)	e AF (%)
Rh (D) positive (167147)	89.136	54.008	45.734	92.614
Rh (D) negative (924)	41.126	93.723	6.280	100.000
Total (168071)	88.872	54.226	45.517	92.654

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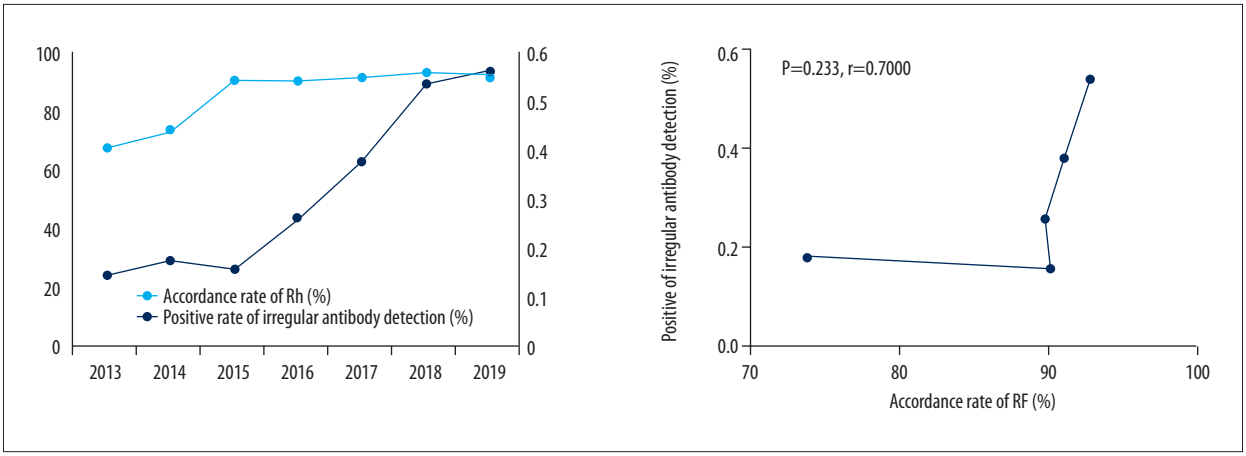

Figure 2. The results of the rate of the Rh 5 major antigens accordance transfusion (accordance of Rh) and the irregular antibody detection: The accordance of Rh was stable at above 90% after 2015, but the positive rate of irregular antibody detection increased year by year. The correlation between the accordance of Rh and the positive rate of irregular antibody detection was not statistically significant (*P*=0.2333, r=0.7000).

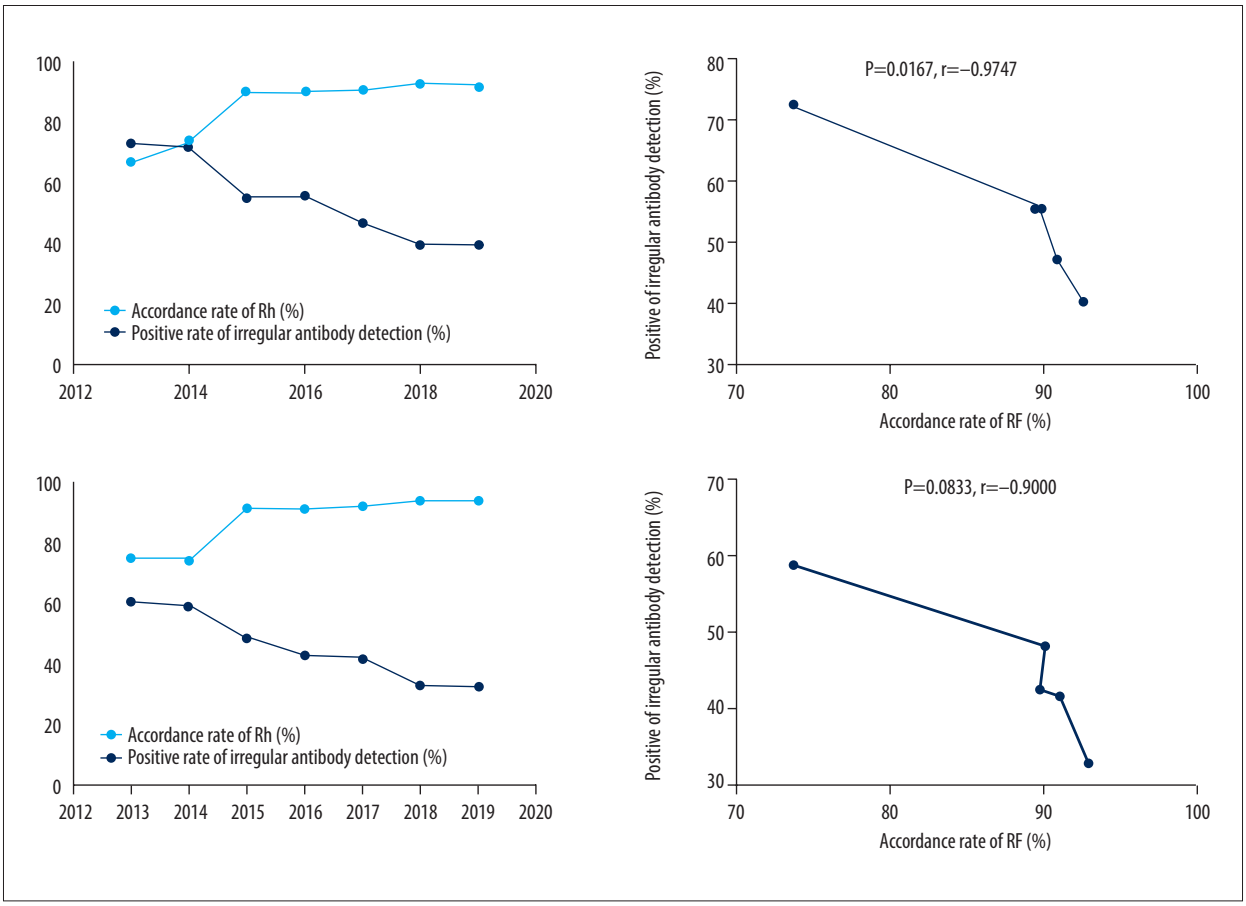

Figure 3. The results of the accordance of Rh and Rh antibody detection: The positive rate of the Rh antibody detection decreased after 2015, and the correlation with the accordance of Rh was statistically significant (*P*=0.0176, r=0.9747). The E antibody of the Rh system was the major antibody. The study results revealed that the correlation with the accordance of Rh was not statistically significant (*P*=0.0833, r=0.9000).

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antigens in this system remained much higher. This can also stimulate the immune system to produce clinically significant antibodies when receiving an infusion of red cells with Rh D, which are compatible and incompatible for C, c, E, or e antigens. However, this might lead to adverse effects from the blood transfusion [16]. Moreover, the specific antibodies of this system were the most frequent antibodies encountered in the pretransfusion testing, which remains the most important reason for hemolytic disease of newborns (HDN) [17].

In the present study, the most common Rh type was CCDee, both in donors and patients, while CcDEe was in second place. These results agree with previously published studies [9,18]. Since these 2 types could reach up to 79.08% in total, these may be a critical factor for the production of alloantibodies and adverse effects of blood transfusion. A total of 27 patients who had adverse effects after blood transfusion in our hospital before 2013 were contacted, and the blood type of the Rh 5 significant phenotypes was analyzed. Among these 27 patients, 15 were CCDee, 9 were CcDee, and 3 were ccDEE. All these patients were given red blood cells of CcDEe. After the development of the homotypic infusion of the Rh 5 major antigens in our department, a decrease in the incident rate of adverse effects was apparent and obvious (Figure 1). All these results show that there is an excellent relationship between the Rh blood group and incidence of adverse effects when there was an incompatible infusion with C, c, E, or e antigens. In addition, some studies reported that the matching for pure antigens (D, C, E, c, e, K, and possibly Fya, Jka, and Jkb) would be successful in preventing alloimmunization in the vast majority of sickle cell disease (SCD) patients [19]. The investigators considered that the rate of adverse effects is very stable at 3%, which might be due to the probability that antigens K, Fya, Jka, and Jkb are not compatible when transfused.

There was a decrease in irregular antibody detection after the accordance of Rh. The accordance of Rh was stable at above 90% after the 2015, but the positive rate of irregular antibody detection increased year by year. These analysis results also show there is a correlation between the accordance of Rh and the positive rate of irregular antibody detection, especially the relationship between the accordance of Rh and the Rh antibody detection. The positive rate of Rh antibody detection decreased after 2015, and the correlation with the accordance of Rh was statistically significant. Also, there is a significant difference ($p<0.05$) in the antibody-positive patients in 8 body systems. As this type of disease is so diverse, it is hard to say which disease easily produces antibody. All these results show that this work has a great effect on patients.

The Duffy antigen is encoded by the FY gene, and the Fya and Fyb antigens are encoded by the FY01 and FY02 alleles [20]. A rearranged RhD allele can encode an altered D antigen, which is the so-called partial D antigen, and an individual homozygous for the rearranged RhD allele or compound heterozygous in trans-silenced RhD allele can produce the anti-D alloantibody [21]. The present study took the partial D antigen as RhD-positive for donors and as RhD-negative for patients. Hence, there is no partial D antigen in the present study.

Limitations of the present study

The major limitation of this study was that only the Rh phenotype and not the Rh genotype of the subjects was tested, but the results are beneficial for clinical work. The other limitation is that there was a higher representation of males in the donors (almost twice the number of females), which is very good for the patients, as the females might have a high antibody rate.

Conclusions

The present study provides guidance in establishing a database of Rh distribution in the population of Hangzhou, Zhejiang province. These results imply that the same Rh phenotype infusion might contribute to the reduction in the incidence rate of adverse effects, and that attention should be focussed not only on the ABO system and RhD phenotype, but also on the other 4 antigens of Rh (C, c, E, and e). The present study can be further extended in the future to include molecular investigations. Finally, merely serological investigations were performed. Molecular probes would be more informative, and should be performed in the future.

Conflict of interests

None.

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Supplementary Data

Supplementary Table 1. Adverse events involving transfusion of different Rh phenotype 2015 to Jun 2019.

Year	Accordance of Rh			Unaccordance of Rh		
	Number of receptors	Number of transfusion	Number of adverse reaction	Number of transfusion		Number of adverse reaction
2015	4871	4389	14	482	90.1	4
2016	4885	4382	13	503	89.7	4
2017	4092	3656	11	436	90	1
2018	4373	4058	12	315	92.8	1
2019.6	2444	2256	7	188	92.3	1
Total	**20665**	**18741**	**57**	**1924**	**90.7**	**11**

Supplementary Table 2. Adverse effects among the patients who received homotypic infusion and the patients who did not receive homotypic infusion from 2015 to Jun 2019.

Year	Number of receptors	Accordance of Rh			Accordance rate of Rh (%)	Discordance of Rh		
		Number of transfusions	Number of adverse reactions	Rate of adverse reaction (‰)		Number of transfusions	Number of adverse reactions	Rate of adverse reaction (‰)
2015	4871	4389	14	3.18	90.1	482	4	8.3
2016	4885	4382	13	2.96	89.7	503	4	7.95
2017	4092	3656	10	2.74	90	436	2	4.59
2018	4373	4058	12	2.96	92.8	315	1	3.17
2019.6	2444	2256	7	3.1	92.3	188	1	5.32
Total	**20665**	**18741**	**56**	**3.04**	**90.7**	**1924**	**12**	**5.72**

Supplementary Table 3. Distribution of antibody-positive patients in the 8 body systems from 2015 to June 2019.

Type of system	Antibody positive	Antibody negative	Antibody positive rate (‰)
Circulatory system	73	2912	24.46
Digestive system	69	2808	23.98
Motor system	39	2637	14.57
Respiratory system	33	2548	12.79
Urinary system	27	2359	11.32
Genital system	18	2267	7.88
Nervous system	30	2411	12.29
Endocrine system	25	2409	10.27
Total	**314**	**20351**	**15.19**

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