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Screening for hemosiderosis in patients receiving multiple red blood cell transfusions

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Abstract

Background: The dramatic impact of hemosiderosis on survival in chronically transfused patients with hereditary anemia is well known. We evaluated whether patients receiving multiple red blood cell (RBC) transfusions are adequately screened for hemosiderosis.

Methods: We retrospectively assessed hemosiderosis screening and prevalence in adult patients that received over twenty RBC units in the University Medical Centre Utrecht from 2010 till 2015. Hemosiderosis was defined as ferritin ≥1000 μg/L. Adequate screening for chronically transfused patients was defined as any ferritin determined up to 3 months before or any moment after the last transfusion, while for patients that received all transfusions within 3 months (bulk transfusion), ferritin had to be determined after at least twenty transfusions.

Results: Of 471 patients, only 38.6% was adequately screened and hemosiderosis prevalence was 46.7%. Hemosiderosis prevalence was 47% in the chronic transfusion group and 12% in the bulk transfusion group. In patients transfused because of hematological malignancy or cardiothoracic surgery, respectively, 74% and 31% were adequately screened and hemosiderosis prevalence was 53% and 13%, respectively.

Conclusion: Hemosiderosis screening in our routine practice is suboptimal. Hemosiderosis is not an exclusive complication of multiple transfusions in the hematology ward. We recommend screening for hemosiderosis in all patients receiving multiple transfusions.

KEYWORDS
blood transfusion, ferritin, hemosiderosis, screening

1 | INTRODUCTION

Hemosiderosis is a type of secondary iron overload resulting from multiple RBC transfusions and the leading cause of death in transfusion-dependent patients with thalassemia.[1] Before the introduction of iron-chelation therapy, the majority of patients with transfusion-dependent beta-thalassemia died between 12 and 24 years of age because of cardiac complications of hemosiderosis.[2]

As iron depletion has been a much greater evolutionary challenge than iron overload, humans have not developed a physiological pathway for iron excretion.[3] Under normal circumstances, the amount of total body iron is approximately 4-5 g, of which 80% is stored in RBCs. One RBC unit contains approximately 200 mg of iron.[4] Therefore, repeated RBC transfusion adds iron to the body rapidly and irreversibly. After transfusion of ten to twenty RBC units symptoms of hemosiderosis can develop.[5,6] Transfusional iron will be stored in the reticulo-endothelial system. When

the storage capacity of this system is exceeded, plasma iron increases and will gradually saturate the iron binding capacity of the natural occurring iron chelator, transferrin. When serum transferrin saturation exceeds 85%, non-transferrin bound iron appears.[7] This non-transferrin bound iron enters the cell through L-type calcium channels and generates reactive oxygen species in organs such as the heart, liver, pituitary gland, and pancreas.[8–10] Finally, the intracellular accumulation of reactive oxygen species will lead to cell damage and ultimately cell death.[11,12] Severe hemosiderosis is characterized by dysfunction of iron overloaded organs resulting in hepatic fibrosis and cirrhosis, cardiac failure and arrhythmias, endocrine pancreatic dysfunction, hypothyroidism, and hypogonadism.[13–15] Consequently, international guidelines recommend screening for hemosiderosis in patients with a history of more than 20 RBC transfusions.[16–20] Particularly in patients with rare anemias receiving chronical transfusion, regular hemosiderosis screening is strongly encouraged.[16–18] However, in patients receiving multiple transfusions for other reasons, for instance trauma or chemotherapy, regular hemosiderosis screening programs have not been implemented very well.

Our hypothesis is that hemosiderosis screening in patients with a history of multiple RBC transfusions is suboptimal. On behalf of the UMC Utrecht Blood Transfusion Committee, we wanted to get more insight into this subject.

Our primary objectives were to (i) evaluate the practice of screening for hemosiderosis in patients who have received more than twenty RBC units in the UMC Utrecht; and (ii) determine the prevalence of hemosiderosis in patients that were adequately screened. Our secondary objective was to identify patient subgroups at risk for hemosiderosis.

2 | METHODS

2.1 | Study population

We conducted an observational, retrospective cohort study to evaluate hemosiderosis screening and prevalence in adult patients with a history of more than 20 RBC transfusions in the University Medical Centre Utrecht (UMC Utrecht, the Netherlands). In the UMC Utrecht electronical medical record systems (laboratory information system GLIMS [MIPS] and hospital medical record system EZIS [Chipsoft]) are used. Patient data are collected in an in-house developed research data platform (RDP). For this study, all data were anonymously collected from this RDP. All eligible patients were included and had data available for review. Eligible were adult patients at risk for hemosiderosis defined as having received more than twenty RBC units in the period January 1, 2010-January 31, 2015. Transfusion indications were obtained via RDP, abstracted from the Hospital Healthcare Cost and Utilization database (Diagnose Behandel Combinatie, DBC). The discharge and visit records in this database contain information collected as part of billing records and *International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)* diagnoses. Furthermore, patient characteristics such as sex, age, death, hospital ward, number of transfused RBC units, number of days between first and last transfusion, the use of iron-chelation therapy, and ferritin levels were collected.

2.2 | Definitions

Time-sensitive variables, such as age, number of transfusions, and death, were determined on January 31, 2015. Guidelines define hemosiderosis as iron accumulation caused by frequent RBC transfusions, reflected by a ferritin level ≥1000 μg/L, with or without organ damage.[6,19,21] Patients were divided in groups according to transfusion indication, hospital ward, and time between first and last transfusion. If all RBC transfusions had been administered within 90 days, the transfusion type was defined as bulk transfusion, if not, the transfusion type was defined as chronic transfusion. In accordance with international guidelines for patients who are chronically transfused, we defined adequate screening as the availability of a ferritin level up to 3 months before or any time after the last transfusion recorded in our database.[16-18] For patients who received bulk transfusion, we defined adequate screening as the availability of a ferritin level after transfusion of at least twenty RBC units. In case of more than one available ferritin level, the most recent measurement was taken. When analyzing our data, it became clear that survival toward the end of the observational period clearly influenced the screening rate for hemosiderosis. Therefore, separate analysis of the data was performed for patients alive at the end of the observational period.

2.3 | Statistical analysis

Medians and interquartile ranges are given for age and number of RBC transfusions. Prevalences and screening rates were compared between groups using the Pearson chi-square test. As a sensitivity analysis, we also evaluated other definitions of adequate screening for hemosiderosis. A *P*-value ≤.05 is considered statistically significant. Statistical analyses were performed with the use of IBM SPSS Statistics software version 22 (IBM Corp., NY, USA).

3 | RESULTS

3.1 | Patients

We identified 471 patients who received more than twenty RBC units. The median age was 62 years, and 65% of the recipient patients was male (Table 1). The most prevalent reason for transfusion was a hematological malignancy (33.5%), followed by cardiothoracic surgery (21.9%). Included patients received a median number of 31 RBC units. Patients with hereditary hemolytic anemia (thalassemia, sickle-cell disease, or not specified) received the most transfusions with a median number of 78 RBC units. Of all patients, most patients (58%) were chronically transfused, while the other 42% received a bulk transfusion. Iron-chelating therapy was prescribed to 40 (8.5%) patients.

3.2 | Hemosiderosis screening and prevalence in all patients

Of all 471 patients, 182 (38.6%) were adequately screened for hemosiderosis (Figure 1). In 115 of 471 (24%) patients, no ferritin level within

TABLE 1 Baseline characteristics of all patients[a]

Characteristic	No. (%) (N=471)	Median RBC units transfused
All patients	471 (100%)	31
Male sex	304 (65%)	30
Median age, y (IQR)	62 (49-70)	
Deceased	249 (53%)	32
Main treating department		
Surgery	232 (49.3%)	32
Hematology	158 (33.5%)	32
Internal medicine	45 (9.6%)	27
Gastroenterology	12 (2.5%)	35
Other	8 (1.7%)	28
Unknown	16 (3.4%)	27
Indication for transfusion[b]		
Hematological malignancy	158 (33.5%)	30
Cardiothoracic surgery	103 (21.9%)	36
Solid tumor	45 (9.6%)	26
Solid organ transplant	38 (8.1%)	35
Aneurysm	25 (5.3%)	27
(Multi)trauma	23 (4.9%)	37
Gastrointestinal bleed	14 (3.0%)	32
Hereditary hemolytic anemia	13 (2.8%)	78
Infection not otherwise specified	9 (1.9%)	25
Infection of liver, pancreas, or gallbladder	8 (1.7%)	28
Hip surgery	7 (1.5%)	26
Hematological disease not otherwise specified	6 (1.3%)	67
Other	21 (4.5%)	27
Unknown	1 (0.2%)	49

IQR, Interquartile range; RBC, red blood cell.

[a]Interquartile ranges for age and number of transfusions are given as there is no normal distribution. All patient characteristics, such as age, number of transfused red blood cell units, and death, were determined on January 31, 2015.

[b]Grouped transfusion indications include (no. between brackets): Hematological malignancy: Acute leukemia (70), myelodysplastic syndrome (27), myeloproliferative disease (19), multiple myeloma (17), lymphoma (10), chronic lymphatic leukemia (7), aplastic anemia (6), chronic myeloid leukemia (2). Solid organ transplant includes lung (27), kidney (11). Hereditary hemolytic anemia includes thalassemia (7), sickle cell (4) and erythrocytic abnormalities not otherwise specified (2). Infection not otherwise specified includes pneumonia (3), sepsis (3), endocarditis (1), meningitis (1), kidney abscess (1). Infection of liver, pancreas, or gallbladder includes hepatitis (2), pancreatitis (3), cholecystitis (3).

3 months of the last transfusion and in 174 of 471 (37%) patients, no ferritin at all was available. In the chronic transfusion group 148 of 273 (54%), patients were adequately screened for hemosiderosis (Table 2). In this group, ferritin levels were not within 3 months of the last transfusion or not determined at all in, respectively, 71 (26%) and 54 (20%) of the patients. In the bulk transfusion group, 34 of 198 (17%) patients were adequately screened for hemosiderosis. In this group, ferritin levels were determined before transfusion of the twentieth RBC unit or not determined at all in, respectively, 42 (21%) and 120 (61%) of the patients. Within the group of adequately screened patients, hemosiderosis prevalence was 46.7% (Figure 1). There were patients that did not fulfill the criteria of adequate screening that nevertheless had prior ferritin levels available. Within these patients, hemosiderosis prevalence was 33 of 113 (29%). Additionally, of the 40 patients on iron-chelating therapy, 18 (45%) patients had ferritin levels that did not fulfill the criteria of hemosiderosis. As a sensitivity analysis, we included all patients on iron-chelating therapy and patients with prior ferritin levels above 1000 μg/L, resulting in an overall hemosiderosis prevalence of 54.9%. In summary, depending on how to address bias such as concurrent interventions to treat hemosiderosis, hemosiderosis prevalence varies between 55% and 47% in our cohort.

3.3 | Hemosiderosis in alive patients

Of all 471 patients, 249 (53%) deceased during the observational period. Deceased patients cannot be screened for hemosiderosis, and some guidelines suggest not to screen patients for hemosiderosis that have a very short life expectancy.[19,22,23] Therefore, we hypothesized that survival to the end of the observational period would influence the screening rate for hemosiderosis. Indeed, the percentage of patients that was screened for hemosiderosis was only 28% (70/249) in the deceased group vs 51% (112/222) in the group alive at the end of the observational period ($P<.001$; Table 2). The prevalence of hemosiderosis differed significantly between alive (39%) and deceased patients (59%, $P=.011$). Because we wanted to limit our report to patients that had a reasonable life expectancy, all further analyses were limited to patients still living at the end of the observational period. Regardless of survival status, screening rates in patients receiving bulk transfusion were significantly lower than in patients that received chronic transfusion (Table 2).

To recognize patient subgroups that could benefit most from screening for hemosiderosis, we identified the different admission wards and transfusion indications of the patients included in our analysis. Depending on hospital ward and the transfusion indication, screening rates for hemosiderosis differed considerably (Table 3). For instance, the percentage of patients that was adequately screened was 78% on the hematology ward and 31% on the surgery ward. Patients that were transfused because of hereditary hemolytic anemia had a 75% screening rate for hemosiderosis. Likewise, 74% of patients that were transfused because of a hematological malignancy were adequately screened. Patients who were transfused for non-hematological transfusion indications, however, were less likely to be screened with a screening rate of 34%. For instance, only 31% of patients who were transfused because of cardiothoracic surgery were adequately screened. As a sensitivity analysis, we limited the analysis to patients that had at least 1 year of follow-up and were alive at the end of follow-up. This did not change the results significantly. In this additional analysis, screening rates were 74% for patients with a hematological malignancy and 67% for patients with hereditary hemolytic anemia.

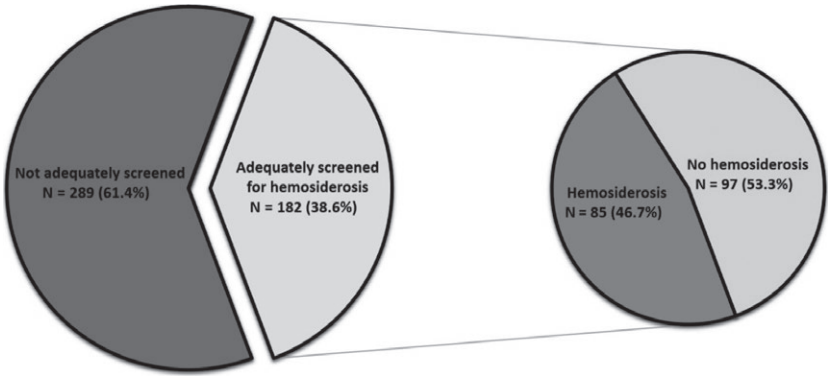

FIGURE 1 Hemosiderosis screening and prevalence in all patients who have received more than 20 red blood cell transfusions. Hemosiderosis is defined as ferritin ≥1000 μg/L

TABLE 2 Hemosiderosis screening and prevalence according to transfusion type[a]

Transfusion type	Adequately screened no./total no. (%)	*P* value[c]	Hemosiderosis no./total no. (%)	*P* value
Bulk	34/198 (17%)	<.001	11/34 (32%)	.063
Chronic	148/273 (54%)		74/148 (50%)	
Alive[b]				
Bulk	25/86 (29%)	<.001	3/25 (12%)	.002
Chronic	87/136 (64%)		41/87 (47%)	
Deceased				
Bulk	9/112 (8%)	.001	8/9 (89%)	.048
Chronic	61/137 (45%)		33/61 (54%)	

[a]Patients are divided in two groups based on transfusion type. A bulk-type transfusion is defined as all transfusions being administered within 90 days, if not, the transfusion type is defined as chronic. For chronically transfused patients, adequate screening for hemosiderosis was defined as the availability of any ferritin level measured after the last transfusion or up to 3 months before the last transfusion. For patients receiving bulk-type transfusion, adequate screening for hemosiderosis was defined as the availability of a ferritin level determined after transfusion of at least twenty RBC units. Hemosiderosis is defined as ferritin ≥1000 μg/L.
[b]Determined on January 31, 2015.
[c]*P*-values were calculated using the Pearson chi-square test.

Hemosiderosis prevalence was 16% at the surgery ward and 54% at the hematology ward (Table 3). Patients that were transfused because of hereditary hemolytic anemia or hematological malignancy had a high prevalence of hemosiderosis (67% and 53%, respectively). In patients that were transfused for non-hematological reasons, there was still a significant percentage of patients (18%) that fulfilled the criteria for hemosiderosis.

The prevalence of hemosiderosis was higher in the chronic-type transfusion group than in the bulk-type transfusion group (12% vs 47%, respectively, *P*=.002; Table 2).

At the surgery ward, the prevalence of hemosiderosis was higher in the chronic-type transfusion group than in the bulk-type transfusion group (31% in the chronic-type transfusion group and 0% in the bulk-type transfusion group, *P*=.02). There was a clear trend with respect to the prevalence of hemosiderosis being higher in the bulk-type transfusion group treated at the hematology ward compared to bulk-type transfusion group treated at the surgery ward (33% vs 0%, respectively, *P*=.05). In chronically transfused patients, the prevalence of hemosiderosis differed significantly between the surgery and hematology ward (respectively, 56% vs 31% in the chronic-type transfusion group, *P*=.025).

4 | DISCUSSION

In this paper, we show that hemosiderosis is not an exclusive complication of multiple transfusion in the hematology ward but also affects patients in other disciplines. Screening for hemosiderosis in multiple transfused patients is suboptimal, while prevalence of hemosiderosis is high. Patients who are chronically transfused are more likely to develop hemosiderosis compared to patients who receive a bulk transfusion. The one subgroup that showed no hemosiderosis are the patients receiving bulk transfusion while admitted at the surgery ward. However, because screening rates in these patients were low, we cannot exclude that hemosiderosis can develop in this subgroup. In contrast, we clearly show that the subgroup of patients receiving chronic transfusions because of a surgical complication, that traditionally is not perceived to be at high risk of developing iron overload, had a prevalence of hemosiderosis as high as 31%.

Hemosiderosis is associated with poor prognosis. As humans have no physiological pathway to excrete excess iron, repeated transfusion inevitably leads to iron overload.[3] In patients with rare hereditary hemolytic anemia who undergo chronic transfusion, iron-induced liver disease and endocrine disorders can develop and are almost

TABLE 3 Hemosiderosis screening and prevalence in alive patients according to main treating department and transfusion indication[a]

	Adequately screened no./ total no. (%)	Hemosiderosis no./total no. (%)
Main treating department		
Total	112/222 (50%)	44/112 (39%)
Surgery	32/105 (31%)	5/32 (16%)
Hematology	67/86 (78%)	36/67 (54%)
Internal medicine	7/11 (64%)	1/7 (14%)
Gastroenterology	2/7 (29%)	0/2 (0%)
Other	2/5 (40%)	0/2 (0%)
Unknown	2/8 (25%)	2/2 (100%)
Transfusion indication		
Hematological overall	67/90 (74%)	36/67 (54%)
Hematological malignancy	53/72 (74%)	28/53 (53%)
Hereditary hemolytic anemia	9/12 (75%)	6/9 (67%)
Hematological disease not otherwise specified	5/6 (83%)	2/5 (40%)
Non-hematological overall	45/132 (34%)	8/45 (18%)
Cardiothoracic surgery	16/51 (31%)	2/16 (13%)
Solid tumor	2/10 (20%)	1/2 (50%)
Solid organ transplant	9/18 (50%)	0/9 (0%)
Aneurysm	1/8 (13%)	0/1 (0%)
(Multi)trauma	1/10 (10%)	0/1 (0%)
Gastrointestinal bleed	3/9 (33%)	0/3 (0%)
Infection not otherwise specified	2/5 (40%)	0/2 (0%)
Infection of liver, pancreas, or gallbladder	2/3 (67%)	2/2 (100%)
Hip surgery	2/7 (29%)	2/2 (100%)
Other	6/10 (60%)	1/6 (17%)
Unknown	1/1 (100%)	0/1 (0%)

[a]Data are presented only for patients alive on January 31, 2015. Hemosiderosis is defined as ferritin ≥1000 μg/L.

inevitably followed by death from iron-induced cardiomyopathy.[24] Better screening and treatment of hemosiderosis has shown to dramatically decrease hemosiderosis-related complications and improve survival among patients with hereditary hemolytic anemia receiving chronic transfusions.[2,25] Likewise, development of hemosiderosis is associated with significantly worse survival in patients with myelodysplastic syndromes and after adjusting for transfusion burden, hazard rates increase by 30% for every 500 μg/L increase in ferritin above the threshold of 1000 μg/L.[6] Treatment is especially recommended for patients with myelodysplastic syndromes having a ferritin ≥1000 μg/L secondary to regular RBC transfusions.[1,23,26.]

For cardiothoracic surgery patients, the effect of hemosiderosis on prognosis is unknown. Most evidence supports the hypothesis that excess iron contributes to chronic disease by fostering excess production of free radicals and there is no reason to assume that surgical patients are exempt from this effect.[27] The strongest suggestion of a causal relation of ferritin in general with cardiovascular outcomes comes from a randomized trial of phlebotomy or no intervention in young patients with peripheral artery disease.[28] In this subgroup of patients, a lower ferritin level predicted improved outcome and iron reduction by phlebotomy improved outcomes by preventing or delaying non-fatal myocardial infarction and stroke. With the clinical experience of the effect of iron overload on cardiac outcome in patients with hereditary hemolytic anemia and the prevalence of hemosiderosis in this patient group in our hospital, there is a strong suggestion to screen these patients better for hemosiderosis. Together, we suggest that there is enough circumstantial evidence to support screening of hemosiderosis in all groups of patients that receive more than twenty RBC transfusions.

International guidelines therefore recommend regular hemosiderosis screening in patients with rare hereditary anemias starting from 10 to 20 RBC transfusions.[16–18] For these patients, it is estimated that the annual per patient costs of iron-induced cardiomyopathy alone is $US14 770.[29] In contrast, the cost of one ferritin measurement is between 1 and 2 euros. To find one case of hemosiderosis, even at the surgery department in our hospital, the number needed to screen is <10. One possible option to improve screening could be a message popping up on the physician's computer after prescription

of the twentieth RBC transfusion, suggesting to order a ferritin level, regardless of hospital ward or transfusion indication.

This study has several limitations. Ideally, we would have excluded patients with a short life expectancy before assessing hemosiderosis screening rates. The Dutch National Hemovigilance Office only recommends screening for hemosiderosis if the patient's life expectancy is more than 1 year.[19] This could explain why patients who were deceased at the end of the observational period were less likely to be screened for hemosiderosis. As a sensitivity analysis, we repeated our analysis in patients that were alive the consecutive year after the last transfusion. This did not change our results significantly, even though we had to exclude patients that received the last transfusion in the last year of the observational period. For example, the proportion of patients with hematological malignancies that was adequately screened remained 74%.

Evidence for hemosiderosis in this cohort study is based on a ferritin level ≥1000 μg/L combined with a history of more than twenty RBC transfusions. The use of ferritin for assessing body iron stores has its limitations as ferritin levels can also be altered by liver disease and inflammation.[30] However, the assessment of ferritin remains the most widely used method for evaluating body iron burden mainly because it is convenient and inexpensive.[31] Moreover, significant correlations between changes in ferritin and liver iron concentration have been reported.[30,32] In addition, current international guidelines for assessing hemosiderosis recommend the use of ferritin.[16–19.]

The definition of the bulk and chronic type of transfusion was made on pragmatic grounds. We hypothesized that 90 days would be a reasonable cutoff as the normal life span of a red blood cell is approximately 4 months.[11] Therefore, transfusion of all RBC units within a 90-day period of time is likely to be associated with some form of blood loss. We are not aware of any literature defining this distinction, although we observed significant differences in hemosiderosis screening and prevalence between these two transfusion types. As expected, we found a lower prevalence of hemosiderosis in patients receiving bulk-type transfusion compared to patients who are chronically transfused. Blood loss is the most plausible indication for RBC transfusion in patients receiving bulk transfusion. These patients should therefore be less prone to develop hemosiderosis compared to patients receiving chronic transfusions. We also found a higher prevalence of hemosiderosis, although not statistically significant, for patients receiving bulk transfusion at the hematology ward compared to patients receiving bulk transfusion at the surgery ward. The explanation could be that patients at the surgery ward are more likely to have some form of blood loss and may therefore be less prone to develop hemosiderosis compared to patients at the hematology ward.

International guidelines recommend that ferritin should be measured every 3 months in patients who receive chronic transfusion.[16–18] Therefore, we defined adequate screening in the chronic transfusion group as the availability of a ferritin level up to 3 months before or any time after the last transfusion recorded in our database. In contrast, for patients in the bulk transfusion group a ferritin measured 3 months before the last transfusion would be irrelevant as this ferritin would have been measured before transfusion of any RBC unit. Therefore, we defined adequate screening in the bulk transfusion group as the availability of a ferritin level measured after transfusion of at least twenty RBC units. In the absence of any guideline regarding hemosiderosis screening in bulk transfusion, we decided twenty RBC units would be a reasonable cutoff as after transfusion of twenty RBC units, symptoms of hemosiderosis can develop.[5,6] Moreover, twenty RBC units is a recommended threshold to start screening for hemosiderosis following international thalassemia guidelines.[16–18.]

The observation that hemosiderosis screening in our hospital is suboptimal while hemosiderosis is prevalent in our patients receiving multiple transfusions is consistent with three previous studies.[33–35] Although these three studies systematically exclude surgical patients, we show that hemosiderosis is not an exclusive complication of multiple transfusion at the hematology ward but can also affect surgical patients. In a recent multicenter observational cross-sectional study in France, Leo-Kodeli et al.[33] showed that 51% (1935/3812) of patients with a history of more than twenty RBC transfusions were screened for hemosiderosis and that hemosiderosis prevalence was 63% (1216/1935) at the hematology ward. Likewise, in a Spanish multicenter observational study, Cid et al.[34] showed that 65% (412/631) of patients with a mean transfusion history of 30 RBC units were screened for hemosiderosis and that hemosiderosis prevalence was 58% (239/412). Similarly, in a small Japanese retrospective study, Ashida et al.[35] showed that in patients with a history of 20 RBC transfusions, hemosiderosis prevalence was 66.2% (43/65). In the Netherlands, transfusion complications such as hemosiderosis are voluntarily reported to the Transfusion Reactions in Patients Dutch National Hemovigilance database. Hemosiderosis has been poorly reported in the Netherlands: Four reports of hemosiderosis were made since 2013.[36.]

In conclusion, we found that screening for hemosiderosis in adult multiple transfused patients in our hospital is suboptimal, while hemosiderosis prevalence is high. Patients who are chronically transfused or transfused at the hematology ward are especially at risk to develop hemosiderosis. More importantly, we found that hemosiderosis is not an exclusive complication of multiple transfusion in the hematology ward but can affect any patient receiving multiple transfusions. We recommend screening for hemosiderosis in all patients receiving multiple transfusions.

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AUTHOR CONTRIBUTIONS

AJ, EB, and RS designed the study. AJ and EB analyzed the data and drafted the manuscript. KV provided data and together with EB and RS critically reviewed the manuscript.

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