Analysis of Risk Factors for Hepatic Sinusoidal Obstruction Syndrome Following Allogeneic Hematopoietic Stem Cell Transplantation in Pediatric Patients

Jaspar Kloehn
Department of Pediatrics, Jena University Hospital, Jena, Germany
Grit Brodt
Department of Pediatrics, Jena University Hospital, Jena, Germany
Jana Ernst
Department of Pediatrics, Jena University Hospital, Jena, Germany
Bernd Gruhn (Bernd.Gruhn@med.uni-jena.de)
Department of Pediatrics, Jena University Hospital, Jena, Germany https://orcid.org/0000-0003-1862-0075

Research Article

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Abstract

Purpose Hepatic sinusoidal obstruction syndrome (SOS), which is also known as veno-occlusive disease of the liver, represents a serious complication following hematopoietic stem cell transplantation (HSCT). Our study aimed to investigate important risk factors for SOS in a pediatric population.

Methods This retrospective study analyzed 105 children who underwent allogeneic HSCT at our pediatric HSCT center in Jena. The observation period was 12 years and SOS was defined by the modified pediatric Seattle criteria up to day +30 after HSCT.

Results 15 out of all 105 patients developed SOS (14.3%). The median time from HSCT to SOS diagnosis was 12 days. The mortality rate of SOS was only 20.0%. In univariate analysis, we identified the significant risk factors of a patient age < 1 year (odds ratio (OR) = 7.25, $p = 0.037$) and a prior treatment with gemtuzumab ozogamicin (OR = 11.00, $p = 0.020$). In addition, some laboratory values, which were taken before HSCT, had a significant association to SOS. Ferritin > 1500 ng/mL (OR = 4.00, $p = 0.033$), ferritin > 2000 ng/mL (OR = 4.69, $p = 0.016$), ferritin > 2400 ng/mL (OR = 5.29, $p = 0.005$) and the international normalized ratio (INR) ≥ 1.3 (OR = 5.91, $p = 0.009$) showed significant results in univariate analysis. The following risk factors could be confirmed in multivariate analysis: prior treatment with gemtuzumab ozogamicin (OR = 9.24, $p = 0.048$), ferritin > 2400 ng/mL (OR = 5.74, $p = 0.023$) and INR ≥ 1.3 (OR = 8.02, $p = 0.007$).

Conclusion Our study confirms several risk factors for hepatic SOS following allogeneic HSCT in pediatric patients. In addition, we report for the first time a significant association between high INR before HSCT and hepatic SOS, which consequently could improve the SOS risk evaluation.

Introduction

Hepatic sinusoidal obstruction syndrome (SOS), previously called veno-occlusive disease (VOD), is one of the potentially life-threatening complications following hematopoietic stem cell transplantation (HSCT).

Pathophysiologically, initial damage to the sinusoidal endothelium leads to an activation of endothelial cells (DeLeve et al. 1999; DeLeve et al. 2002). This damage is caused by factors like chemotherapy or radiotherapy as part of the conditioning regimen before HSCT. The unregulated endothelial activation results in a loss of sinusoidal barrier, leading to extravasation of erythrocytes, leukocytes and cellular debris into the space of Disse. Moreover, a cascade of thrombotic and antithrombotic effects causes a hemostatic dysbalance. The damaged sinusoids induce a downstream embolization, sinusoidal obstruction, and occlusion of terminal hepatic venules (Carreras and Diaz-Ricart 2011; Coppell et al. 2003; Mohty et al. 2015).

The frequency of SOS varies widely in the published literature depending on different diagnostic criteria (Carreras et al. 2011; Coppell et al. 2010; Kammersgaard et al. 2019). Coppell et al. (2010) showed a mean incidence of 13.7% for SOS following HSCT by analyzing different reports of SOS occurring with a

range from 0–62%. Traditional diagnostic standards are based on the Baltimore criteria, reported by Jones et al. (1987), or the Seattle criteria, reported by McDonald et al. (1984). The Seattle criteria have been modified several times. The modified pediatric Seattle criteria, attributed to Corbacioglu et al. (2012), are presented in Table 1. These citeria depend on the clinical findings hyperbilirubinemia (> 34 µmol/L; > 2 mg/dL)), hepatomegaly, ascites and unexplained weight gain (> 5%) (Corbacioglu et al. 2012). Recently, new diagnostic criteria have been published on behalf of the European Society for Blood and Marrow Transplantation (EBMT) to achieve an earlier identification and to detect late-onset SOS. Mohty et al. (2016) developed the EBMT criteria for SOS in adult patients. Furthermore, Corbacioglu et al. (2018) published the pediatric EBMT criteria. In addition to the EBMT criteria, Cairo et al. (2020) proposed modified diagnostic criteria. In the past years, different criteria for severity grading were published (Bearman et al. 1993; Cairo et al. 2020; Corbacioglu et al. 2018; McDonald et al. 1993; Mohty et al. 2016). In common the most severe form of SOS can lead to multi-organ dysfunction with a mortality rate of up to 84% (Coppell et al. 2010).

The most promising therapeutic option for SOS is the use of defibrotide, which was shown in several studies for both adult and pediatric patients (Chopra et al. 2000; Corbacioglu et al. 2004; Locatelli et al. 2020; Richardson et al. 1998; Richardson et al. 2002; Richardson et al. 2016; Richardson et al. 2013). Additionally, the prophylactic effect of defibrotide was described (Corbacioglu et al. 2012; Qureshi et al. 2008).

The known risk factors for SOS can be classified into patient-related factors and transplantation-related factors (Corbacioglu et al. 2019; Dalle and Giralt 2016). Patient-related factors include young patient age, preexisting liver disease, advanced malignant underlying diseases, treatment with gemtuzumab ozogamicin, high transaminase levels, high serum ferritin and genetic factors (Carreras et al. 1998; Cheuk et al. 2007; Maximova et al. 2014; McDonald 2002; Morado et al. 1999; Seifert et al. 2015). Reported transplantation-related risk factors are allogeneic HSCT, conditioning regimen based on busulfan, cyclophosphamide, fludarabine or total body irradiation and unrelated donors (Barker et al. 2003; Carreras et al. 1998; Carreras et al. 2011).

Even though some risk factors are already known, it is important to confirm these results and to analyze new potential risk factors. This will lead to better risk stratification and earlier identification of SOS. The purpose of our study was to evaluate the risk factors of SOS in pediatric patients undergoing allogeneic HSCT.

Patients And Methods

Patients

Our retrospective study included 105 children, adolescents and young adults who underwent allogeneic HSCT at the Department of Pediatrics of Jena University Hospital in Germany. We only analyzed recipients after the first HSCT. Patients who received a defibrotide prophylaxis were excluded. The transplantations were performed between January 2007 and December 2018. All patients underwent a

myeloablative conditioning regimen and were nursed in single rooms with a laminar airflow filtration system.

Definitions

SOS was defined by using the modified pediatric Seattle criteria up to day +30 after HSCT (Corbacioglu et al. 2012). These criteria include hyperbilirubinemia (> 34 µmol/L; > 2 mg/dL), hepatomegaly, ascites and unexplained weight gain (> 5%). The diagnosis of SOS was confirmed when at least two of the mentioned criteria were met within 30 days after HSCT. The classification of the severity of SOS was based on the severity criteria by McDonald et al. (1993) in consideration of later modifications. SOS was defined as mild when patients had no apparent adverse effect from SOS, did not need diuretic or analgesic therapy, and showed completely reversible clinical and laboratory abnormalities. The moderate stage was characterized by clinical worsening following SOS or the need for diuretic or analgesic therapy. Patients with moderate SOS showed a full recovery within 100 days. Any clinical worsening without recovery within 100 days, as well as the occurrence of multiple organ failure or even death, was classified as severe SOS.

Risk factors

In our study, we considered patient-related factors, including several laboratory parameters, and transplantation-related factors. Some analyzed factors were already known to be associated with SOS. Moreover, we investigated new potential risk factors. The following transplantation-related factors were included in our study: conditioning regimen based on busulfan, cyclophosphamide, melphalan or total body irradiation, graft source, donor age, donor sex and donor-recipient human leukocyte antigen (HLA)-match. In addition, we explored the following patient-related factors: patient age, patient sex, prior treatment with gemtuzumab ozogamicin as well as the laboratory parameters of aspartate transaminase, alanine transaminase, cholinesterase, glutamyl transpeptidase, lactate dehydrogenase, alkaline phosphatase, ferritin, albumin, total bilirubin, C-reactive protein and international normalized ratio (INR). All laboratory values were determined before HSCT. Furthermore, cutoffs were chosen for metric variables such as age and laboratory parameters. These cutoffs were defined by reference values, clinical consideration and receiver operating characteristic (ROC) curve analysis.

Statistical analysis

To evaluate the association between the analyzed factors and the occurrence of SOS, univariate and multivariate analyses were performed. *P*-values of less than 0.05 indicated statistical significance. The results for each variable were expressed as odds ratios (OR) with their 95% confidence intervals (CI). ROC curve analysis was used to determine adequate cutoffs. Univariate analyses were carried out by chi-square test or Fisher's exact test. Moreover, the Mann-Whitney U-test was used to compare the median values of metric variables. Variables that were significant in the univariate analyses were entered into multivariate analysis. The multivariate analysis was performed by backward stepwise logistic regression. All calculations were performed by the software IBM SPSS Statistics 26.

Results

Patient characteristics

The characteristics of the 105 patients are presented in Table 2. The study population consisted of 61 males and 44 females with a median age of 8.6 years (ranged from 0 to 26 years). Either bone marrow (n = 74) or peripheral blood (n = 31) was used as stem cell source. The most frequent underlying diseases were acute lymphoblastic leukemia (n = 27), acute myeloid leukemia (n = 25) and genetic disease (n = 25).

Incidence and mortality of SOS

SOS occurred in 15 out of 105 transplantations (14.3%). The median time of the SOS diagnosis was 12 days after HSCT (range 1–26 days). Mild SOS occurred in 3 cases, moderate SOS in 4 cases, while 8 patients showed a severe form. Among the 15 patients with SOS, 3 subsequently died (20.0%). These 3 patients died within the first 100 days after HSCT. In contrast, 5 out of 90 patients without the diagnosis of SOS died in this period, which results in a 100-day mortality of only 5.6%.

Analysis of risk factors

The Tables 3 and 4 display the univariate analysis of transplantation-related and patient-related factors. We could not find any significant association between transplantation-related factors and the occurrence of SOS. However, several significant patient-related risk factors could be identified in our study. Patients aged less than 1 year had a significantly higher rate of SOS compared to older patients (50.0% vs. 12.1%, OR = 7.25, $p = 0.037$). Additionally, prior treatment with gemtuzumab ozogamicin was significantly associated with the incidence of SOS (OR = 11.00, $p = 0.020$). The SOS rate in patients treated with gemtuzumab ozogamicin was 60.0% compared to 12.0% in the group without such treatment. By comparing the pretransplant serum levels of ferritin in patients with and without SOS, a significantly higher median ferritin was found in patients who developed SOS (2816.9 ng/mL vs. 1554.0 ng/mL, $p = 0.026$). Different cutoffs for serum ferritin were analyzed by a ROC curve (Fig. 1). A cutoff value of 2420.15 ng/mL (see arrow in Fig. 1) indicated the best result for sensitivity (73.3%) and specificity (65.8%). To put this cutoff into clinical practice, it was rounded to a value of 2400 ng/mL. Patients with serum ferritin > 2400 ng/mL showed a significantly higher incidence of SOS compared to those with ferritin ≤ 2400 ng/mL (29.7% vs. 7.4%, OR = 5.29, $p = 0.005$). Furthermore, ferritin > 1500 ng/mL (OR = 4.00, $p = 0.033$) and ferritin > 2000 ng/mL (OR = 4.69, $p = 0.016$) were significant risk factors. I addition, we noted a significant correlation between pretransplant INR ≥ 1.3 and the occurrence of SOS (OR = 5.91, $p = 0.009$). Patients with INR ≥ 1.3 showed a SOS rate of 37.5%. In contrast, the SOS rate was 9.2% in patients with lower INR.

As presented in Table 5, the following factors were significant in our multivariate analysis: prior treatment with gemtuzumab ozogamicin (OR = 9.24, $p = 0.048$), ferritin > 2400 ng/mL (OR = 5.74, $p = 0.023$) and INR ≥ 1.3 (OR = 8.02, $p = 0.007$).

Discussion

In our study, 15 out of 105 patients developed SOS. Consequently, the incidence of SOS was 14.3%. In a previous study, which compared different incidence rates of SOS across several studies an overall mean incidence of 13.7% was reported (Coppell et al. 2010). This demonstrates that our result is consistent with previous data. In our study population, the median time of SOS onset was 12 days after HSCT, which corresponds to the literature. Yakushijin et al. (2016) retrospectively analyzed 4290 patients who underwent allogeneic HSCT. In that study, the median time of SOS diagnosis was also 12 days post-HSCT (Yakushijin et al. 2016). The frequencies of mild, moderate and severe SOS have been variously reported. From all patients with SOS, we observed a relative distribution of 20.0% mild, 26.7% moderate and 53.3% severe disease courses. In a study published by Cheuk et al. (2007), 47.4% had mild SOS, 21.1% had moderate SOS and 31.6% had severe SOS. However, Maximova et al. (2014) reported a rate of 12.0% mild, 12.0% moderate and 76.0% severe courses of SOS. In all cases, the same criteria for severity grading based on McDonald et al. (1993) were used. Furthermore, all studies only included pediatric patients. This variation can be explained by a different interpretation of the severity grading criteria or small case numbers. In the present study, the mortality rate from SOS was only 20.0%, which is a lower rate, especially compared to previous studies (Barker et al. 2003; Cheuk et al. 2007; Jones et al. 1987; McDonald et al. 1993). The lower mortality rates in recent studies are probably due to the early treatment with defibrotide (Corbacioglu et al. 2016; Faraci et al. 2019; Mohty et al. 2020; Richardson et al. 2017).

The diagnosis of SOS was based on the modified pediatric Seattle criteria according to Corbacioglu et al. (2012). In recent years, new diagnostic criteria have been published (Cairo et al. 2020; Corbacioglu et al. 2018; Mohty et al. 2016). Additionally, new severity criteria were proposed. In our study, we decided not to use these new criteria because nearly all transplantations had been performed before the new pediatric EBMT criteria were published (Corbacioglu et al. 2018). By using the new EBMT criteria, the number of diagnosed SOS cases would be probably higher, especially due to no limitation for the time of SOS onset (Kammersgaard et al. 2019). Therefore, we preferred a consistent use of the modified pediatric Seattle criteria.

Previous publications have already shown significant associations between the transplantation-related factors of conditioning regimen based on busulfan or total body irradiation and the occurrence of SOS (Barker et al. 2003; Carreras et al. 1998; Cheuk et al. 2007; Yakushijin et al. 2016). On the contrary, these reported risk factors were not found to be significant in our study. One reason for this result can be the limited number of analyzed patients. Nevertheless, other studies also could not find a significant correlation (Kami et al. 1997; Maximova et al. 2014).

A significant relationship between an increased risk of SOS and donor mismatch has already been reported (Hasegawa et al. 1998). We could not confirm this finding in our patient population. Other transplantation-related factors like stem cell source, donor age and donor sex were not significantly associated with the incidence of SOS either. Carreras et al. (2011) showed a significantly higher rate of SOS in transplantations with bone marrow stem cells compared to transplantations with peripheral blood

stem cells. A few other analyses could not find a significant correlation between the stem cell source and the development of SOS (Cheuk et al. 2007; Faraci et al. 2019; Soyer et al. 2020; Strouse et al. 2018). In future trials, this potential risk factor should be further explored.

With regards to younger patients, we found that an age < 1 year had a significant impact on the development of SOS in the univariate analysis ($p = 0.037$). Full hepatic maturation takes up to 2 years after birth (Beath 2003). This demonstrates that infants have a reduced hepatic detoxification function, which consequently makes them particularly vulnerable to the conditioning regimen. Thus, higher rates of SOS could be explained. Moreover, pediatric diseases that are predisposing to SOS are found more often in the first years of life (Cesaro et al. 2005). This especially applies to neuroblastoma. Our findings concur with the published literature although different cutoffs for age were proposed (Cesaro et al. 2005; Cheuk et al. 2007; Faraci et al. 2019).

In our study, we could not find a significant correlation between female sex and the incidence of SOS. According to our results, this factor was not listed in some detailed reviews (Cairo et al. 2020; Dalle and Giralt 2016). However, other studies identified female sex as a significant risk factor (Faraci et al. 2019; Hägglund et al. 1998). This aspect should be further investigated in future trials.

Previous reports have already highlighted the treatment with gemtuzumab ozogamicin as a risk factor for SOS incidence (McDonald 2002; Richardson and Corbacioglu 2020; Wadleigh et al. 2003). It is assumed that gemtuzumab ozogamicin targets CD33 + cells in the hepatic sinusoids, such as Kupffer cells, stellate cells and endothelial cells (Rajvanshi et al. 2002). Our study confirms the significant risk factor of prior treatment with gemtuzumab ozogamicin for the pediatric population in univariate analysis ($p = 0.020$) as well as in multivariate analysis ($p = 0.048$).

In the literature, some studies showed significant correlations between SOS and elevated values of aspartate transaminase, alanine transaminase and total bilirubin as well as reduced values of cholinesterase and albumin (Carreras et al. 1998; Hägglund et al. 1998; Hasegawa et al. 1998; Srivastava et al. 2004). These values indicate preexisting liver damage. However, we could not find such significant associations in our patient population. According to the current state of relevant studies, the laboratory parameters of glutamyl transpeptidase, lactate dehydrogenase, alkaline phosphatase, C-reactive protein were not significant risk factors (Cairo et al. 2020; Corbacioglu et al. 2019; Dalle and Giralt 2016; Morado et al. 1999). In regard to serum ferritin, we detected significantly higher SOS rates in patients with ferritin > 1500 ng/mL, > 2000 ng/mL and > 2400 ng/mL. However, > 2400 ng/mL was the optimal cutoff with $p = 0.005$ in univariate analysis and $p = 0.023$ in multivariate analysis. High serum ferritin indicates iron overload, which is considered to be a reason for liver dysfunction (McKay et al. 1996; Miceli et al. 2006). Iron induces the development of oxygen free radicals that lead to an injury of hepatic tissue (Ramm and Ruddell 2005). Additionally, high serum ferritin can be explained by the response to inflammation through its role as an acute-phase protein (Armand et al. 2012). It can be suggested that these factors predispose to SOS. Our findings accord with other studies (Maradei et al. 2009; Maximova et al. 2014; Morado et al. 1999).

In our study, we report for the first time that high pretransplant INR was significantly associated with the occurrence of SOS. The cutoff of ≥ 1.3 was significant in univariate analysis ($p = 0.009$) as well as in multivariate analysis ($p = 0.007$). Higher INR values indicate increased bleeding tendency (Kirkwood 1983). Although SOS is characterized by downstream embolization and sinusoidal obstruction, there is an initial hemorrhage of erythrocytes, leukocytes and cellular debris into the spaces of Disse (Carreras and Diaz-Ricart 2011; Mohty et al. 2015). Therfore, an increased bleeding tendency, measured by high INR, could lead to a higher risk of SOS. Moreover, INR is affected by vitamin K-dependent coagulation factors (Tripodi et al. 1995). High INR can be caused by a lack of coagulation factors, which is linked with liver dysfunction. This is another reason why high INR might be correlated to SOS.

Our study is limited by the relatively small number of patients, which leads to reduced statistical power. However, the rather small number of patients is quite common in single-center studies with only pediatric patients. I addition, our study is a retrospective analysis which is more susceptible to observation and selection biases compared to prospective studies. Nevertheless, the inclusion criteria were clearly defined and consistently used.

In conclusion, our findings confirm the risk factors of young patient age (< 1 year), prior treatment with gemtuzumab ozogamicin and high serum ferritin (> 2400 ng/mL) for the occurrence of hepatic SOS in the pediatric population. Furthermore, the significant association between high pretransplant INR (≥ 1.3) and the development of SOS is reported for the first time. Our findings can contribute to a better risk stratification and a modified screening system after allogeneic HSCT in pediatric patients. Finally, further studies are necessary to validate our findings. This especially applies to the new risk factor of high INR.

Declarations

Compliance with ethical standards

Conflict of interest The authors declare no potential conflict of interest.

Ethical standard All procedures were in accordance with the ethical standards. The study was approved by the ethics committee at the University Hospital of the Friedrich Schiller University at Jena (2021-2060). Informed consent was obtained from all individual participants or the responsible persons included in the study.

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Tables

Table 1
Modified pediatric Seattle criteria for the diagnosis of SOS

Modified Seattle criteria
Presence of at least 2 of the following within 30 days after HSCT:
Bilirubin > 34 µmol/L (> 2 mg/dL)
Hepatomegaly
Ascites
Unexplained weight gain > 5%
According to Corbacioglu et al. (2012); Hematopoietic stem cell transplantation (HSCT)

Table 2
Characteristics of patients and donors

Characteristics	No.
Patients (%)	105 (100)
Median age, years (range)	8.6 (0–26)
Male (%)	61 (58.1)
Female (%)	44 (41.9)
Donors	
Median age, years (range)	28.5 (0–54)
Male (%)	63 (60.0)
Female (%)	42 (40.0)
Patients' diagnoses	
Acute lymphoblastic leukemia (%)	27 (25.7)
Acute myeloid leukemia (%)	25 (23.8)
Myelodysplastic syndrome (%)	14 (13.3)
Lymphoma (%)	2 (1.9)
Solid tumor (%)	12 (11.4)
Genetic disease (%)	25 (23.8)
Stem cell source	
Bone marrow (%)	74 (70.5)
Peripheral blood (%)	31 (29.5)
Type of donors	
HLA-compatible unrelatad (%)	52 (49.5)
HLA-mismatched unrelated (%)	20 (19.0)
HLA-haploidentical related (%)	18 (17.1)
HLA-identical related (%)	15 (14.3)

Number (No.); Human leukocyte antigen (HLA)

Table 3
Univariate analysis of transplantation-related factors

Transplantation-related factors	No.	SOS	OR	95% CI	*p*
Busulfan					
Yes	45	8 (17.8%)	1.64	0.55–4.91	0.376
No	60	7 (11.7%)	–	–	–
Busulfan plus cyclophosphamide or melphalan					
Yes	31	5 (16.1%)	1.23	0.38–3.95	0.764
No	74	10 (13.5%)	–	–	–
Total body irradiation					
Yes	19	4 (21.1%)	1.82	0.51–6.48	0.466
No	86	11 (12.8%)	–	–	–
Stem cell source					
Bone marrow	74	13 (17.6%)	3.09	0.65–14.60	0.221
Peripheral blood	31	2 (6.5%)	–	–	–
Donor age					
≤ 28 years	46	9 (19.6%)	3.24	0.82–12.91	0.082
> 28 years	43	3 (7.0%)	–	–	–
Donor sex					
Female	42	7 (16.7%)	1.38	0.46–4.13	0.569
Male	63	8 (12.7%)	–	–	–
HLA-mismatch					
No	67	10 (14.9%)	1.16	0.36–3.68	0.804
Yes	38	5 (13.2%)	–	–	–

Number (No.); Sinusoidal obstruction syndrome (SOS); Odds ratio (OR); Confidence interval (CI); Human leukocyte antigen (HLA)

Table 4
Univariate analysis of patient-related factors

Patient-related factors	No.	SOS	OR	95% CI	*p*
Patient age					
< 1 year	6	3 (50.0%)	7.25	1.31–40.10	**0.037**
≥ 1 year	99	12 (12.1%)	–	–	–
Patient sex					
Female	44	7 (15.9%)	1.25	0.42–3.76	0.686
Male	61	8 (13.1%)	–	–	–
Gemtuzumab ozogamicin					
Yes	5	3 (60.0%)	11.00	1.67–72.68	**0.020**
No	100	12 (12.0%)	–	–	–
Aspartate transaminase					
> 1 µmol/L*s	10	2 (20.0%)	1.48	0.28–7.83	0.643
≤ 1 µmol/L*s	83	12 (14.5%)	–	–	–
Alanin transaminase					
> 1 µmol/L*s	28	5 (17.9%)	1.46	0.78–10.89	0.538
≤ 1 µmol/L*s	77	10 (13.0%)	–	–	–
Cholinesterase					
< 90 µmol/L*s	21	5 (23.8%)	1.80	0.51–6.30	0.497
≥ 90 µmol/L*s	54	8 (14.8%)	–	–	–
Glutamyl transpeptidase					
≤ 0,5 µmol/L*s	44	9 (20.5%)	2.11	0.65–6.88	0.210
> 0,5 µmol/L*s	46	5 (10.9%)	–	–	–
Lactate dehydrogenase					
> 5 µmol/L*s	9	2 (22.2%)	1.78	0.33–9.52	0.616
≤ 5 µmol/L*s	94	13 (13.8%)	–	–	–

Number (No.); Sinusoidal obstruction syndrome (SOS); Odds ratio (OR); Confidence interval (CI)

Patient-related factors	No.	SOS	OR	95% CI	*p*
Alkaline phosphatase					
> 3 µmol/L*s	13	4 (30.8%)	3.38	0.88–13.03	0.085
≤ 3 µmol/L*s	86	10 (11.6%)	–	–	–
Ferritin					
> 2400 ng/mL	37	11 (29.7%)	5.29	1.53–18.25	**0.005**
≤ 2400 ng/mL	54	4 (7.4%)	–	–	–
Ferritin					
> 2000 ng/mL	47	12 (25.5%)	4.69	1.22–17.95	**0.016**
≤ 2000 ng/mL	44	3 (6.8%)	–	–	–
Ferritin					
> 1500 ng/mL	50	12 (24.0%)	4.00	1.05–15.32	**0.033**
≤ 1500 ng/mL	41	3 (7.3%)	–	–	–
Albumin					
< 30 g/L	62	9 (14.5%)	1.02	0.33–3.11	0.974
≥ 30 g/L	42	6 (14.3%)	–	–	–
Total bilirubin					
> 17 µmol/L	28	5 (17.9%)	1.46	0.45–4.71	0.538
≤ 17 µmol/L	77	10 (13.0%)	–	–	–
C-reactive protein					
> 18 mg/L	40	8 (20.0%)	2.07	0.69–6.24	0.189
≤ 18 mg/L	65	7 (10.8%)	–	–	–
International normalized ratio					
≥ 1,3	16	6 (37.5%)	5.91	1.65–21.19	**0.009**
< 1,3	76	7 (9.2%)	–	–	–

Number (No.); Sinusoidal obstruction syndrome (SOS); Odds ratio (OR); Confidence interval (CI)

Table 5

Multivariate analysis of risk factors

Risk factors in multivariate analysis	OR	95% CI	*p*
Gemtuzumab ozogamicin	9.24	1.02-83.55	**0.048**
Ferritin > 2400 ng/mL	5.74	1.27-26.04	**0.023**
INR ≥ 1.3	8.02	1.77-36.43	**0.007**

Odds ratio (OR); Confidence interval (CI); International normalized ratio (INR)

Figures

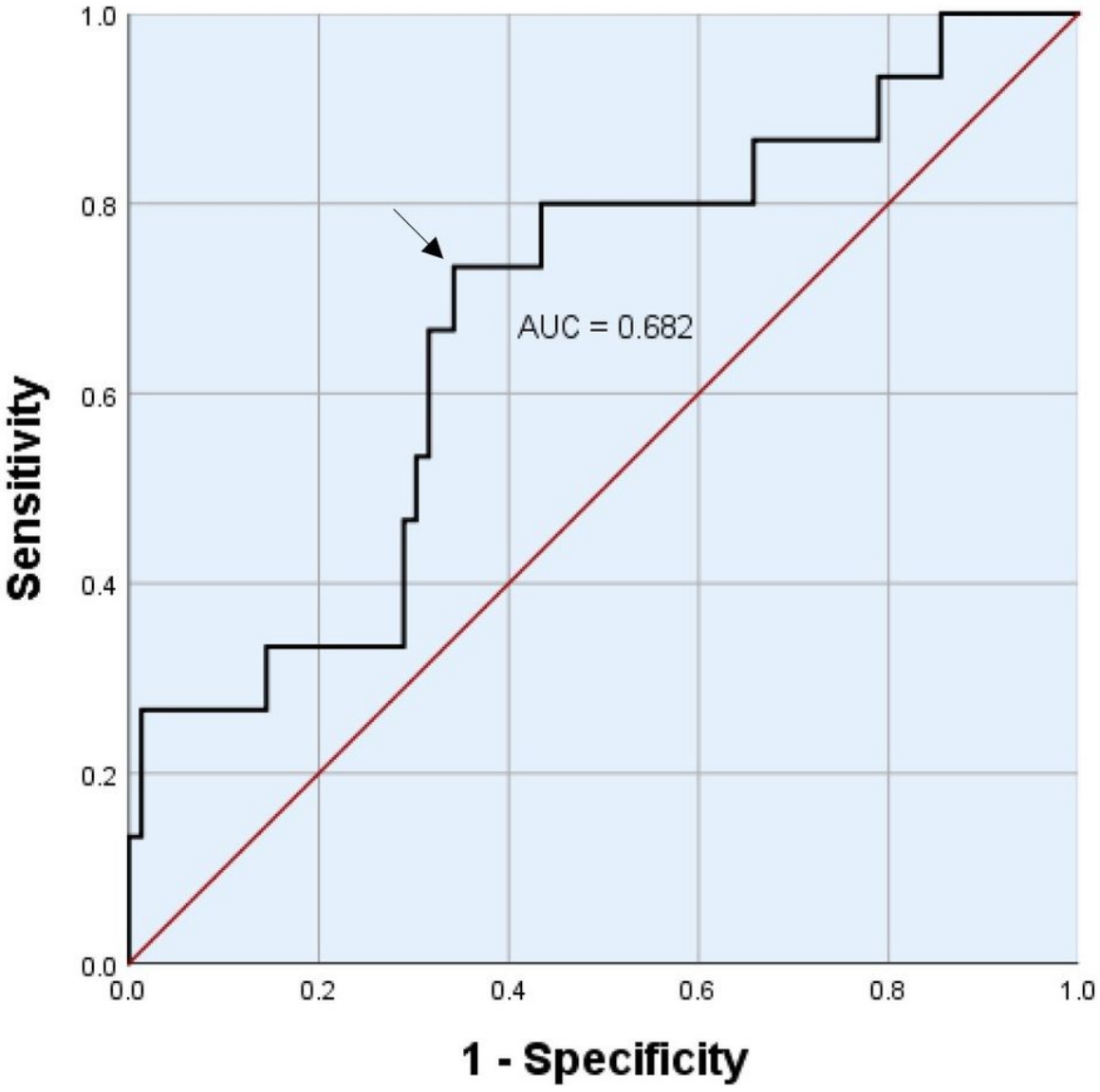

Figure 1

Receiver operating characteristic curve of different ferritin cutoffs Best ferritin cutoff is marked with an arrow (2420.15 ng/mL); Area under the curve (AUC)