Research Square

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Hemolysis and Iron Metabolism in the Context of IMPELLA Management

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Abstract

Background and Purpose

Hemolysis is a common and significant complication associated with Impella implantation, primarily attributed to shear stress. This retrospective study investigates the potential relationship between iron metabolism and hemolysis in patients with Impella devices to better understand the underlying mechanisms of this complication.

Materials and Methods

This study analyzed patients who underwent Impella implantation between 2018 and 2023. Iron metabolism and hemolysis were assessed using transferrin saturation (TSAT) and serum transferrin levels. Multivariate analysis was adjusted for body surface area, pulmonary artery pulsatility index, an aortic and mitral annulus angle of less than 125 degrees, left ventricular end-diastolic dimension, and maintenance pump level.

Results

Sixty-one patients with a mean age of 68 ± 11.8 years were included. Among these patients, 55.7% had a TSAT greater than 20%, with 20.7% in the hemolysis group and 87.5% in the non-hemolysis group. Average transferrin levels were 195 mg/dL (range: 173–249 mg/dL), with higher levels observed in the hemolysis group (245 mg/dL; 218–267 mg/dL) compared to the non-hemolysis group (179.5 mg/dL; 164–194 mg/dL). Multivariate logistic regression analysis revealed significant associations between hemolysis in Impella patients and TSAT (odds ratio [OR] = 0.03, 95% confidence interval [CI]: 0.00–0.18) and transferrin levels (OR = 19.6, 95% CI: 3.48–111).

Conclusions

The findings provide preliminary evidence of a potential link between iron metabolism and hemolysis in patients receiving Impella support. However, further exploration and validation through large-scale, prospective studies are required to establish the strength and consistency of this association.

1. Introduction

Currently, the Impella device is anticipated to improve the survival rates of patients suffering from cardiogenic shock [1]. The Ganger Shock Trial reported that in patients with ST-Elevation Myocardial Infarction (STEMI) who also suffer from cardiogenic shock but have a stable level of consciousness, the use of Impella improved hard endpoints compared to standard treatments [2]. However, the overall effectiveness of Impella in cardiogenic shock has yet to be proven, presenting a significant challenge in clinical practice [3]. A potential contributing factor to this uncertainty could be the high incidence of complications associated with using Impella. Achieving and sustaining hemodynamic stability with Impella can be challenging due to potential complications such as hemolysis, hemorrhage, vascular

injury, and stroke [4]. In particular, hemolysis may cause acute kidney injury and require renal replacement therapy [5, 6]. Moreover, hemolysis may prevent the elevation of Impella pump levels to high settings, thus impeding the device's effectiveness. Therefore, it is urgent to investigate the causes of hemolysis. Previously, it has been reported that the angles of the aortic and mitral valves are important factors in hemolysis during the use of Impella [7]. Additionally, hemodynamic factors such as the pulmonary artery pulsatility index (PAPi) have been reported to correlate with hemolysis [8]. Hemolysis associated with Impella is primarily attributed to shear stress and impaired blood flow, which can generally be mitigated through the appropriate implantation of the device [9]. From a biochemical perspective, a positive correlation exists between shear stress and blood viscosity, suggesting that elevated transferrin levels due to iron deficiency may increase blood viscosity [10]. This mechanism could influence the occurrence of hemolysis during the use of the Impella device. Thus, we conducted a study at our institution to explore the potential relationship between Impella-induced hemolysis and iron metabolism.

2. Methods

2.1 Study population and data collection

This retrospective cohort study, conducted with strict adherence to ethical standards, was performed at a single center. The study cohort included patients who required Impella support for cardiogenic shock at our institution between August 2018 and March 2023. Patients undergoing dialysis were excluded due to the difficulty in assessing hemolysis through urine analysis. Additionally, patients receiving both Impella and extracorporeal membrane oxygenation (ECMO) were excluded to eliminate ECMO-induced hemolysis as a confounding factor. Patient confidentiality was strictly maintained during data collection and analysis. Blood samples were obtained immediately before Impella initiation, and Swan-Ganz catheter data were collected while the Impella pump level was stable. Ethical approval was granted by the Ethics Committee of Iwate Medical University (MH2022-052), and informed consent was obtained from all participants.

Cardiogenic shock was defined according to the Society for Cardiovascular Angiography and Interventions (SCAI) criteria, stages C to E [11]. Hemolysis was defined as the presence of dark red urine, lactate dehydrogenase (LDH) levels exceeding 1.5 times the normal upper limit, anemia confirmed by blood tests, and elevated total bilirubin levels with a corresponding increase in indirect bilirubin [7]. Upon confirmation of hemolysis, fluid management was reassessed using echocardiography and right heart catheterization. Iron metabolism was assessed using transferrin saturation (TSAT) and serum transferrin levels, with TSAT calculated as (serum iron/total iron-binding capacity) × 100%. Left ventricular ejection fraction was measured via transthoracic echocardiography using the modified Simpson method. In accordance with prior studies, a narrow angle between the aortic and mitral annulus was defined as < 126.5° [7].

2.2 Statistical Analysis

Continuous variables are presented as medians with interquartile ranges for non-normally distributed data, while categorical variables are presented as frequencies and percentages. Group comparisons for continuous variables were performed using the t-test for normally distributed data and the Kruskal–Wallis test for non-normally distributed data. The chi-squared test was used to compare categorical variables. The primary endpoint was the occurrence of hemolysis. Kaplan-Meier analysis was employed to compare TSAT levels and time to hemolysis between groups, with significance assessed by the log-rank test. Receiver operating characteristic (ROC) analysis was used to determine optimal cutoff values for TSAT and transferrin levels. Kaplan-Meier analyses with log-rank tests were subsequently used to compare transferrin cutoff values and time to hemolysis. Multivariate logistic regression was conducted to assess the association between iron metabolism and hemolysis, adjusting for body surface area (BSA), PAPi, narrow angle (< 125°), left ventricular end-diastolic dimension (LVDD), and Impella pump level. Statistical analysis was performed using EZR (version 4.2.2) [12], with p-values < 0.05 considered statistically significant.

3. Results

3.1. Baseline Characteristics of the Study Population

This study initially enrolled 90 patients. After excluding two patients undergoing hemodialysis, 11 patients on ECMO, and 16 patients with incomplete data, a total of 61 patients were included in the final analysis. Table 1 presents the baseline characteristics of the study population. Hemolysis occurred in 29 out of the 61 patients managed with Impella. The median age of the participants was 70 years (63–74), with 27.9% being female. The distribution of Impella types was as follows: 18% for 2.5, 80.3% for CP, and 1.6% for 5.0. In this study, 34 patients (55.7%) had a TSAT greater than 20%, with 6 patients (20.7%) in the hemolysis group and 28 patients (87.5%) in the non-hemolysis group. Transferrin levels averaged 195 mg/dL (173–249 mg/dL) overall, with higher levels in the hemolysis group at 245 mg/dL (218–267 mg/dL) compared to 179.5 mg/dL (164–194 mg/dL) in the non-hemolysis group. The maintenance pump level was consistently 6 (4–6) across all patients but varied between groups: 4 (3–6) in the hemolysis group and 6 (4–8) in the non-hemolysis group. The cohort experiencing hemolysis exhibited a larger BSA, higher iron levels, higher total iron-binding capacity (TIBC), a higher percentage of patients with TSAT values below 20%, significantly elevated transferrin levels, and lower maintenance pump levels. However, no significant differences were observed in PAPi or the narrow-angle between the groups.

Table 1
Baseline chactersistics

	Total	Hemolysis group	Non - hemolysis group	P value
Number	61	29	32	
Age	70 (63–74)	71 (65–76)	69 (60.5–73)	0.54
male, n (%)	44 (72.1)	22 (75.9)	22 (68.8)	0.58
Height (cm)	163 (156–170)	167 (160–171)	162.5 (155–167)	0.15
Body surface area (m^2)	1.63 (1.49–1.88)	1.73 (1.57–1.9)	1.55 (1.42–1.72)	< 0.01
Acute coronary syndrome, n (%)	40 (65.6)	22 (75.9)	18 (56.2)	0.18
Systolic blood pressure (mmHg)	82 (75–100)	85 (75–92)	80 (74.75–101)	0.6
Diastolic blood pressure (mmHg)	61 (57–70)	61 (59–70)	61 (55.25–70)	0.7
Heart rate (bpm)	104 (83–120)	108 (86–120)	103.5 (74.5–118.25)	0.32
Support duration (days)	5 (3–8)	5 (3–8)	4.5 (3–9)	0.93
CHDF[a], n (%)	15 (24.6)	9 (31)	6 (18.8)	0.37
LVEF[b] (%)	33 (27–42)	32 (29–42)	34 (26–42)	0.94
LVDD[c] (mm)	48 (43–53)	46 (44–54)	49 (42–53)	0.72
The narrow-angle[d], n (%)	35 (57.4)	19 (65.5)	16 (50)	0.3
PAWP[e] (mmHg)	17 (14–20)	18 (15–24)	15.5 (14–19.25)	0.05
Mean PAP[f] (mmHg)	25 (21–30)	24 (22–30)	26.5 (20.25–30.75)	0.83

Values are expressed as median (25–75%) or number of subjects (percentage).

$p < 0.05$ by Fisher's exact test as appropriate.

[a]Continuous hemodiafiltration, [b]Left ventricular ejection fraction, [c]Left ventricular end-diastolic dimension, [d]The patient with angle of aortic and mitral annulus < 125°, [e]Pulmonary artery wedge pressure, [f]Pulmonary artery pressure, [g]Right atrium pressure, [h]Pulmonary artery pulsatility index, [i]Creatinine kinase, [j]estimated glomerular filtration rate, [k]Total iron binding capacity, [l]Transferrin saturation

	Total	Hemolysis group	Non - hemolysis group	P value
RAP[g] (mmHg)	10 (8–13)	11 (8–12)	8.5 (6–13)	0.28
PAPi[h]	1.77 (1.3–2.2)	1.75 (1.09–2)	1.81 (1.44–2.34)	0.37
Cardiac index (L/min/m^2)	2.3 (1.9–2.5)	2.2 (1.8–2.4)	2.4 (2.08–2.5)	0.19
Hemoglobin (g/dl)	13.5 (11.7–15.3)	13.7 (11.8–15.4)	13.35 (11.67–15.15)	0.49
Maximum CK[i] (IU/L)	7281 (4057–13583)	8473 (4565–13760)	7000 (3867–12491)	0.42
eGFR[j] (ml/min/1.73m^2)	53 (30.1–67.1)	56.7 (31.5–71.8)	51.3 (29.93–63.67)	0.44
Lactic acid (mmol/L)	3.3 (2.3–4.9)	3.3 (2.3–5.1)	3.35 (2.3–4.8)	0.72
Iron (µg/dL)	54 (39–65)	49 (37–55)	57.5 (45–68.25)	0.01
TIBC[k] (µg/dL)	233 (198–279)	268 (215–304)	216 (181.5–257.25)	< 0.01
Transferrin (mg/dL)	195 (173–249)	245 (218–267)	179.5 (164–194)	< 0.01
Ferritin (ng/mL)	262 (169–398)	219 (102–470)	270 (197–338)	0.29
TSAT[l] >20%, n (%)	34 (55.7)	6 (20.7)	28 (87.5)	< 0.01
Maintenance Pump level	6 (4–6)	4 (3–6)	6 (4–8)	< 0.01
Impella device type				
Impella 2.5, n (%)	11 (18)	5 (17.2)	6 (18.8)	0.99
Impella CP, n (%)	49 (80.3)	24 (82.8)	25 (78.1)	0.75
Impella 5.0, n (%)	1 (1.6)	0 (0)	1 (3.1)	-

Values are expressed as median (25–75%) or number of subjects (percentage).

$p < 0.05$ by Fisher's exact test as appropriate.

[a]Continuous hemodiafiltration, [b]Left ventricular ejection fraction, [c]Left ventricular end-diastolic dimension, [d]The patient with angle of aortic and mitral annulus < 125°, [e]Pulmonary artery wedge pressure, [f]Pulmonary artery pressure, [g]Right atrium pressure, [h]Pulmonary artery pulsatility index, [i]Creatinine kinase, [j]estimated glomerular filtration rate, [k]Total iron binding capacity, [l]Transferrin saturation

Table 2
Correlates of elevated Hemolysis group using logistic regression analysis

Variable	Model 1		Model 2	
	OR (95%CI)	P value	OR (95%CI)	P value
TSAT[a] >20	0.04 (0.01–0.15)	< 0.01	0.03 (0.00–0.18)	< 0.01
Transferrin ≥ 218	22 (5.71–84.8)	< 0.01	19.6 (3.48–111)	< 0.01
$p < 0.05$				
Model 1: Univariate analysis.				
Model 2: Adjusted for body surface area, left ventricular end-diastolic dimension, the angle of aortic and mitral annulus < 125, pulmonary artery pulsatility index, and maintenance pump level.				
[a]Transferrin saturation				

3.2. Association of TSAT and Transferrin with Hemolysis in Impella Patients

The Kaplan-Meier curve illustrating the relationship between time to hemolysis and TSAT in patients using Impella demonstrated a significantly higher incidence of hemolysis in the TSAT ≤ 20% group, with a marked increase in hemolysis within 5 days ($p < 0.01$, Fig. 1). ROC analysis determined the cutoff for transferrin to be 218 mg/dL, with an area under the curve of 0.837 (Fig. 2). A comparison of hemolysis incidence between groups with transferrin levels above and below 218 mg/dL confirmed a significant association, with a higher incidence in the group with transferrin levels above 218 mg/dL ($p < 0.01$, Fig. 3).

3.3. Iron Metabolism and Associated Factors in Hemolysis

Univariate logistic regression analysis revealed a positive association between transferrin levels ≥ 218 mg/dL and hemolysis (OR = 22, 95% CI: 5.71–84.8, $p < 0.01$). Conversely, TSAT > 20% was negatively correlated with hemolysis (OR = 0.04, 95% CI: 0.01–0.15, $p < 0.01$). Furthermore, multivariate logistic regression analysis, incorporating BSA, LVDD, the narrow-angle, PAPi, maintenance pump level, and transferrin, revealed a positive correlation between hemolysis and transferrin (OR = 19.6, 95% CI: 3.48–111, $p < 0.01$). Similarly, analysis including BSA, LVDD, the narrow-angle, PAPi, maintenance pump level, and TSAT > 20% demonstrated a negative correlation between hemolysis and TSAT > 20% (OR = 0.03, 95% CI: 0.00–0.18, $p < 0.01$).

4. Discussion

In this study, we examined the relationship between hemolysis and iron metabolism in 61 patients who received Impella devices at our hospital. In the hemolysis group, TSAT showed a negative correlation with hemolysis, while transferrin levels showed a positive correlation. Although the Impella device

provides effective circulatory support at higher pump levels, hemolysis may necessitate reduced settings, making hemolysis management critical for optimal device performance. Previous studies have associated hemolysis with structural factors such as the angle between the mitral and aortic valves and hemodynamic factors like PAPi [7, 8]. Our study is the first to identify biochemical factors contributing to hemolysis in Impella patients.

The negative correlation between TSAT and hemolysis, and the positive correlation with transferrin levels, remained significant after adjusting for LVDD, indicating minimal fluid volume influence. Prior studies have linked increased blood viscosity during ECMO use to hemolysis [13–15], with hyperglycemia and red blood cell deformation identified as key contributors [16, 17]. Iron deficiency anemia has also been associated with higher blood viscosity [18], and transferrin may elevate viscosity through coagulation effects [19]. These insights highlight the potential of optimizing iron metabolism to mitigate hemolysis, although large-scale prospective studies are needed to confirm these findings due to our study's retrospective design and small sample size.

While our study observed a trend toward narrower aortic-mitral angles in the hemolysis group, no statistically significant differences were found. However, the inclusion of the narrow-angle in multivariate analysis did not alter the relationship between iron kinetics and hemolysis, suggesting an independent link between iron metabolism and hemolysis in Impella patients. Additionally, the hemolysis group had a PAPi of 1.75 (1.09–2), indicating good right heart function, which contrasts with previous reports and may explain the lack of association between hemolysis and PAPi in our study.

Given the complexity of managing Impella in cardiogenic shock patients, integrating hemodynamic, anatomical, and biochemical factors such as iron metabolism is essential. Further prospective research is necessary to enhance management strategies and improve outcomes in Impella-supported patients.

5. Limitations

This study is a single-center retrospective cohort. Dialysis patients were excluded due to the inability to confirm the definition of hemolysis in this group, leaving the relationship between hemolysis and iron kinetics during Impella use in dialysis patients unclear and warranting further research. Most cases in this study exhibited relatively preserved right heart function, and the relationship between iron kinetics and hemolysis in cases with impaired right heart function remains unknown. This study hypothesized that iron kinetics could influence red blood cell viscosity, potentially increasing the likelihood of hemolysis. However, no established evidence currently demonstrates a direct link between iron metabolism and hemolysis, and whether iron metabolism directly contributes to hemolysis or if other factors related to iron kinetics are involved remains an area for future investigation.

6. Conclusion

This study suggests a potential association between iron metabolism and hemolysis in patients undergoing Impella management. However, it does not explore whether iron metabolism predisposes

patients to hemolysis. Further validation through large-scale prospective studies is necessary to confirm the extent and robustness of this association.

Abbreviations

STEMI: ST-Elevation Myocardial Infarction

PAPi: Pulmonary artery pulsatility index

ECMO: Extracorporeal membrane oxygenation

SCAI: The Society for Cardiovascular Angiography and Interventions

LDH: Lactate dehydrogenase

TSAT: Transferrin saturation

ROC: Receiver operating characteristic

BSA: Body surface area

LVDD: Left ventricular end-diastolic dimension

TIBC: Total iron-binding capacity

Declarations

Ethics approval and consent to participate

We received ethical approval from the Ethics Committee of Iwate Medical University (MH2022-052) and obtained informed consent from all participants. This study was conducted in accordance with the principles of the Declaration of Helsinki.

Clinical trial number

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no conflicts of interest.

Footnotes

All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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None.

Author Contribution

H.K. designed the study, contributed to data collection, performed data analysis and interpretation, wrote the first draft of the manuscript, and contributed to critical revisions. T.N., K.T., R.N., and Y.M. contributed to critical revisions of the manuscript.

Availability of data and material

The datasets analyzed in the current study are not publicly available due to ethical reasons but are available upon request after approval from the Ethical Committee of Iwate Medical University.

References

1. Basir B M, Kapur K N, Patel K, et al. Improved Outcomes Associated with the use of Shock. Protocols: Updates from the National Cardiogenic Shock Initiative. Catheter Cardiovasc Interv. 2019;1-11.
2. Møller JE, Engstrøm T, Jensen LO, et al. Microaxial Flow Pump or Standard Care in Infarct-Related Cardiogenic Shock. N Engl J Med. 2024;390:1382-1393.
3. Schrage B, Ibrahim K, Loehn T, et al. Impella Support for Acute Myocardial Infarction Complicated by Cardiogenic Shock. Matched-Pair IABP-SHOCK II Trial 30-Day Mortality Analysis. Circulation. 2019;139:1249-1258.
4. Zein R, Patel C, Alamo M A, et al. A Review of the Impella Devices. Interv Cardiol. 2022;17:e05.
5. Esposito L M, Morine J K, Annamalai K S, et al. Increased Plasma-Free Hemoglobin Levels Identify Hemolysis in Patients With Cardiogenic Shock and a Transvalvular Micro-Axial Flow Pump. Artif Organs. 2019;43(2):125-131.
6. Qian Q, Nath A K, Wu Y, et al. Hemolysis and Acute Kidney Failure. Am J Kidney Dis 56:780-784.
7. Nakamura M, Imamura T, Fukui T, et al. Impact of the angle between aortic and mitral annulus on the occurrence of hemolysis during Impella support. J Artif Organs. 2020;23:207-213.
8. Nakamura M, Imamura T, Hida Y, and Kinugawa K. Pulmonary Artery Pulsatility Index and Hemolysis during Impella-Incorporated Mechanical Circulatory Support. J. Clin. Med. 2022;11:1206.
9. Roberts N, Chandrasekaran U, Das S, et al. Hemolysis associated with Impella heart pump positioning: In vitro hemolysis testing and computational fluid dynamics modeling. Int J Artif Organs. 2020;43(11):710-718.

10. Tang X, Fang M, Cheng R, et al. Iron-Deficiency and Estrogen Are Associated With Ischemic Stroke by Up-Regulating Transferrin to Induce Hypercoagulability. Circ. Res. 2020;127:651-663.
11. Baran A D, Grines L C, Bailey S, et al. SCAI clinical expert consensus statement on the classification of cardiogenic shock. This document was endorsed by the American College of Cardiology (ACC), the American Heart Association (AHA), the Society of Critical Care Medicine (SCCM), and the Society of Thoracic Surgeons (STS) in April 2019. Catheter Cardiovasc Interv. 2019;94:29-37.
12. Kanda Y. Investigation of the freely available easy-to-use software 'EZR' for medical statistics. Bone Marrow Transplant. 2013;48:452-458.
13. Chu H J, Sarathy S, Ramesh S, et al. Risk factors for hemolysis with centrifugal pumps in pediatric extracorporeal membrane oxygenation: Is pump replacement an answer? Perfusion. 2023;38(4):771-780.
14. Venado A, Wille K, Belott S C, and Guzman D E. Unexplained hemolysis in patients undergoing ECMO: beware of hypertriglyceridemia. Perfusion. 2015;30(6):465-468.
15. Pan Y, Li Y, Li Y, and Chen H. Fatigue of red blood cells under periodic squeezes in ECMO. Proc. Natl. Acad. Sci. U.S.A. 2022;119(49)e2210819119.
16. Cho I Y, Mooney P M, and Cho J D. Hemorheological Disorders in Diabetes Mellitus. J Diabetes Sci Technol. 2008;2(6):1130-1138.
17. Czaja M, Kabat M, and Wasilewski J. **Hemorheological Parameters and Fibrinogen in Atherosclerosis. J Cardiol Ther. 2014;1(9):206-211.**
18. Mora M L, Fusares C M, Torres F J, et al. Blood Rheological Characterization of β-Thalassemia Trait and Iron Deficiency Anemia Using Front Microrheometry. Front. Physiol. 2021;12:761411.
19. Tang X, Zhang Z, Fang M, et al. Transferrin plays a central role in coagulation balance by interacting with clotting factors. Cell Res. 2020;30:119-132.

Figures

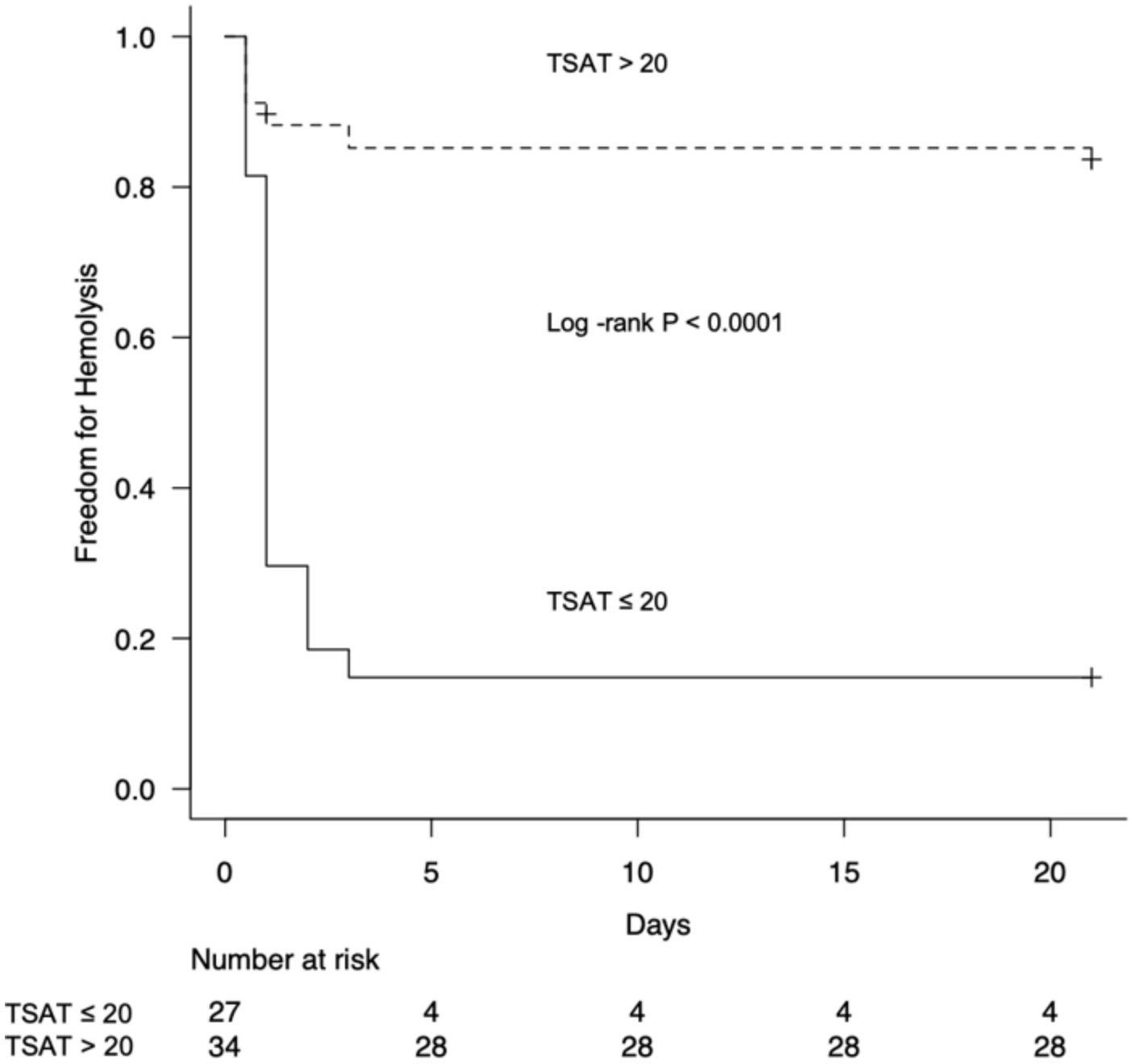


Figure 1

Hemolysis in patients with Impella: TSAT level comparison using Kaplan-Meier Curves

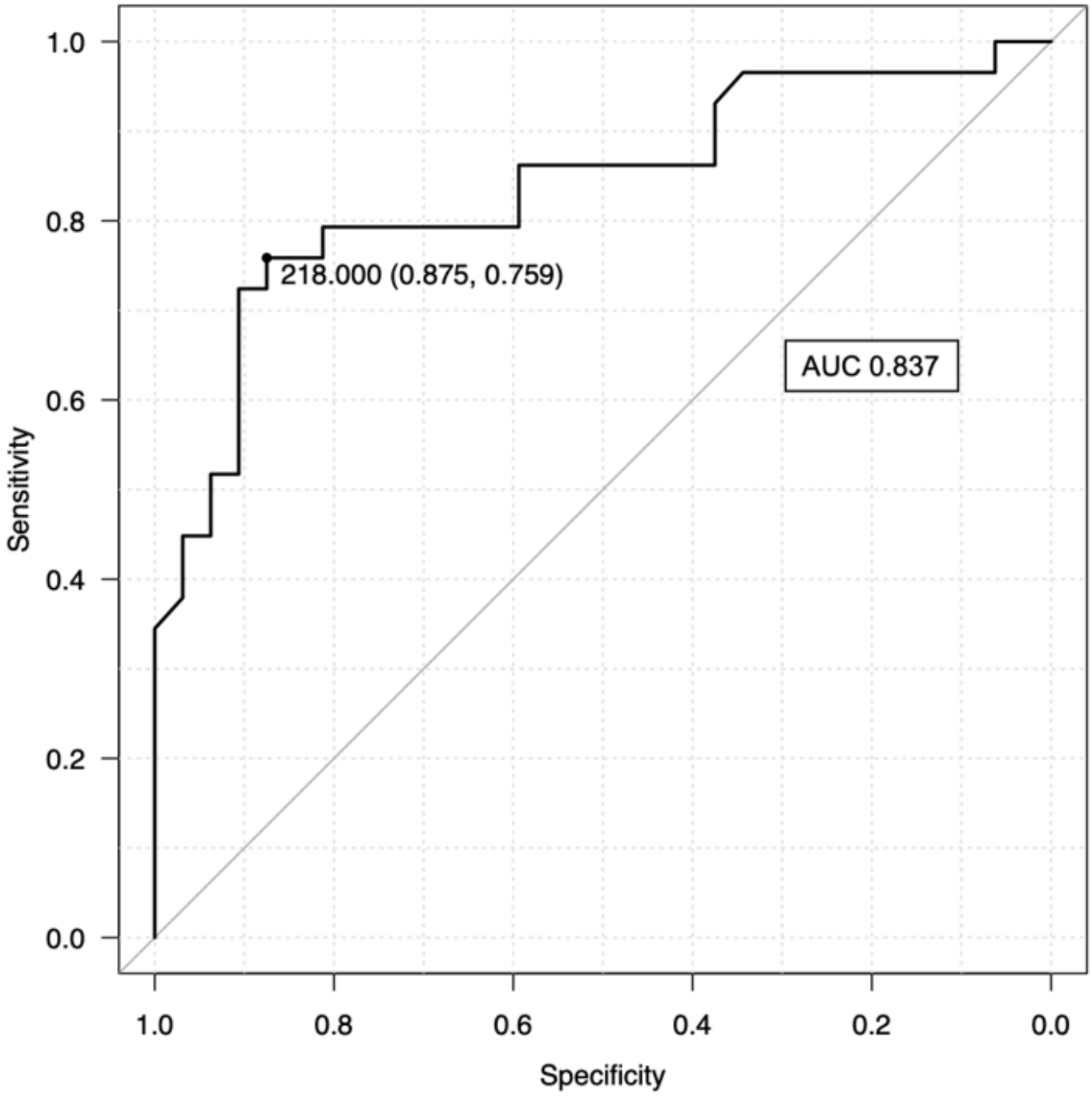


Figure 2

Transferrin levels in hemolytic events with Impella : A ROC curve analysis

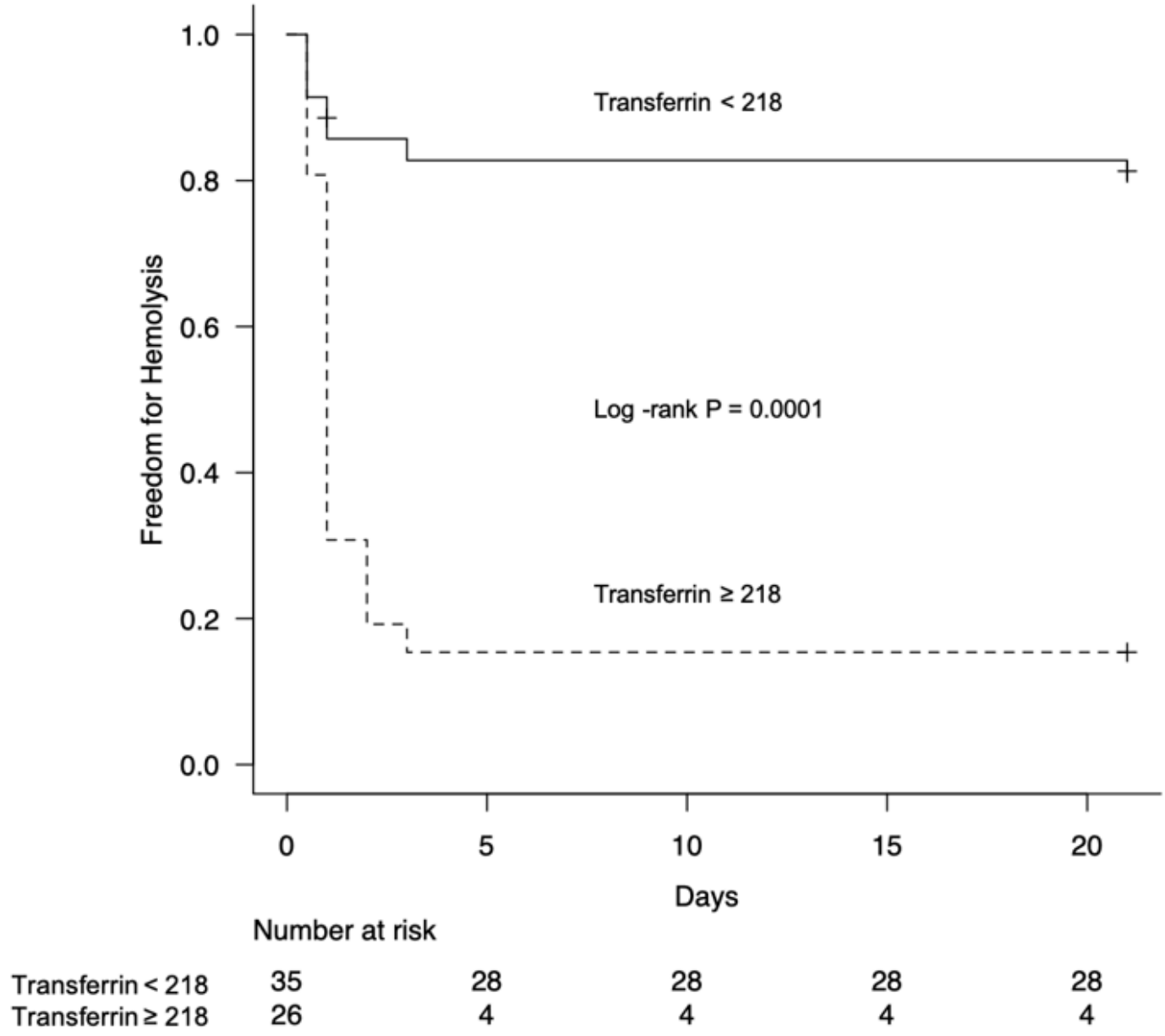


Figure 3

Hemolysis in patients with Impella: Transferrin level comparison using Kaplan-Meier Curves.