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Heparin-Induced Thrombocytopenia in Patients Suffering Cardiogenic Shock

OBJECTIVES: Cardiogenic shock (CS) is associated with high mortality. Patients treated for CS mostly require heparin therapy, which may be associated with complications such as heparin-induced thrombocytopenia (HIT). HIT represents a serious condition associated with platelet decline and increased hypercoagulability and remains a poorly researched field in intensive care medicine. Primary purpose of this study was to: 1) determine HIT prevalence in CS, 2) assess the performance of common diagnostic tests for the workup of HIT, and 3) compare outcomes in CS patients with excluded and confirmed HIT.

DESIGN: Retrospective dual-center study including adult patients 18 years old or older with diagnosed CS and suspected HIT from January 2010 to November 2022.

SETTING: Cardiac ICU at the Ludwig-Maximilians University hospital in Munich and the university hospital of Bonn.

PATIENTS AND INTERVENTIONS: In this retrospective analysis, adult patients with diagnosed CS and suspected HIT were included. Differences in baseline characteristics, mortality, neurologic and safety outcomes between patients with excluded and confirmed HIT were evaluated.

MEASUREMENTS AND MAIN RESULTS: In cases of suspected HIT, positive screening antibodies were detected in 159 of 2808 patients (5.7%). HIT was confirmed via positive functional assay in 57 of 2808 patients, corresponding to a prevalence rate of 2.0%. The positive predictive value for anti-platelet factor 4/heparin screening antibodies was 35.8%. Total in-hospital mortality (58.8% vs. 57.9%; $p > 0.999$), 1-month mortality (47.1% vs. 43.9%; $p = 0.781$), and 12-month mortality (58.8% vs. 59.6%; $p > 0.999$) were similar between patients with excluded and confirmed HIT, respectively. Furthermore, no significant difference in neurologic outcome among survivors was found between groups (Cerebral Performance Category [CPC] score 1: 8.8% vs. 8.8%; $p > 0.999$ and CPC 2: 7.8% vs. 12.3%; $p = 0.485$).

CONCLUSIONS: HIT was a rare complication in CS patients treated with unfractionated heparin and was not associated with increased mortality. Also, HIT confirmation was not associated with worse neurologic outcome in survivors. Future studies should aim at developing more precise, standardized, and cost-effective strategies to diagnose HIT and prevent complications.

KEYWORDS: argatroban; cardiogenic shock; heparin-induced thrombocytopenia; thrombocytopenia

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Cardiogenic shock (CS) is a state of reduced cardiac output accompanied by signs of end-organ hypoperfusion associated with high mortality (1, 2). Despite therapeutic advancements and growing knowledge from randomized clinical trials, overall prognosis remains poor (3–5). Patients treated in the ICU for CS are at risk for various complications such as thrombocytopenia and consecutive bleeding, especially when mechanical circulatory support (MCS) is required (5–7). Common causes of thrombocytopenia in

KEY POINTS

Questions: Primary purpose of this study was to: 1) determine HIT prevalence in cardiogenic shock (CS), 2) assess the performance of common diagnostic tests for the workup of HIT, and 3) compare outcomes in CS patients with excluded and confirmed HIT.

Findings: In this retrospective dual-center study, HIT was prevalent in 2.0 % of CS patients treated with unfractionated heparin (UFH) therapy and was not associated with increased mortality. Survivors of CS with confirmed HIT did not show worse neurologic outcome.

Meaning: HIT in CS represents a rare complication of UFH therapy and future studies should aim to provide more precise, standardized, and cost-effective strategies to diagnose HIT and prevent complications.

the ICU include bleeding with consecutive increased platelet consumption, sepsis, adverse drug reactions, or platelet consumption due to interaction of platelets with extracorporeal surfaces during MCS (8).

Most patients in the ICU require prophylactic or therapeutic unfractionated heparin (UFH) treatment; thus, heparin-induced thrombocytopenia (HIT) should also be considered as an important differential diagnosis in thrombocytopenic patients. HIT is an immune-mediated serious adverse effect of heparin treatment caused by platelet-activating anti-platelet factor 4 (PF4)/heparin antibodies. This condition is characterized by a reduction in platelet count greater than 50% from baseline 5–10 days following exposure to heparin, evidence of specific heparin-dependent immunoglobulin G (IgG) antibodies, and new onset thrombosis (9). HIT is a challenging clinical emergency because UFH treatment must be stopped immediately and alternative anticoagulation begun, leaving patients at risk for both thrombosis and potential bleeding complications. Thus, rapid and effective laboratory diagnosis is essential. Diagnosis is further complicated by lack of real-world standardization in the initiation of HIT diagnostics. Additionally, clinical scores such as the HIT-4T score, which determines the pretest probability of HIT, have not been validated in CS patients. Also, the reliability of antibody search tests in this context remains unknown. Although previous studies have analyzed HIT in general ICU populations and in those undergoing MCS, there is limited data regarding the prevalence, diagnosis, management, and outcomes in patients with suspected and confirmed HIT suffering from CS (10–13).

Considering the clinical relevance of HIT and the substantial differences in baseline characteristics and treatment strategies between CS patients and other ICU (sub)populations, the purpose of this dual-center retrospective analysis was to: 1) determine the prevalence of HIT in CS, 2) assess the performance of common tests for the diagnostic workup of HIT, and 3) compare clinical outcomes in CS patients with excluded and confirmed HIT.

METHODS

Study Design, Ethics Approval, and Patient Selection

This dual-center retrospective study included adult patients 18 years old or older with diagnosed CS and suspected HIT admitted to the cardiac ICU at the Ludwig-Maximilians University (LMU) hospital in Munich, Germany and the university hospital of Bonn, Germany between January 2010 and November 2022. Data were anonymized after extraction from the LMUshock registry (World Health Organization International Clinical Trials Registry Platform DRKS00015860) and patient records from the university hospital of Bonn. CS was defined as a systolic blood pressure less than 90 mm Hg for greater than 30 minutes or catecholamine requirement to maintain a systolic blood pressure greater than 90 mm Hg, signs of pulmonary congestion, and at least one of the following: altered mental status, dizziness, cold and clammy skin or extremities, oliguria (urine output < 30 mL/hr), narrow pulse pressure, metabolic acidosis, elevated serum lactate (> 2 mmol/L), or elevated creatinine due to cardiac dysfunction. Data collection and analysis were performed in accordance with the Declaration of Helsinki and German data protection laws. The study was approved by the local ethics committee (Institutional Review Board number: 23-0295, approval date: May 10, 2023, title: Heparin-induced thrombocytopenia in patients suffering cardiogenic shock). Patients with a history of HIT upon admission were excluded, and data were collected by

one senior clinician at each site. Subsequent proof of validity and integrity of the dataset was assessed by one senior ICU physician and the Institute of Medical Information Processing, Biometry, and Epidemiology statistical team at LMU Munich. Statistical analysis was prespecified, and statistical analysis planning was written before data were received by the statistical analysis team. Primary analysis of the data compiled exclusively for the present study complied with Strengthening the Reporting of Observational Studies in Epidemiology criteria.

Study Outcomes

Primary outcome variables included HIT prevalence, in-hospital mortality, 1-, and 12-month mortality as well as functional outcome of survivors measured by Cerebral Performance Category score (ranging from 1 point [normal neurologic function] to 5 points [brain death]). Further outcome variables included platelet count over the course of ICU stay, positive predictive value (PPV) of HIT antibody screening tests, and safety and efficacy of an alternative anticoagulation strategy.

Anticoagulation During Cardiogenic Shock

Standardized anticoagulation protocols were applied for all patients treated with UFH according to indication. Dose of UFH, which was applied by continuous IV infusion, was adapted four times daily according to activated partial thrombin time (aPTT) measurements. In case of bleeding, interruption or dose adjustment was applied according to the discretion of the responsible intensivist. Heparin-bonded circuits were used in all patients requiring venoarterial extracorporeal membrane oxygenation (ECMO).

HIT Diagnosis and Clinical Management

For all CS patients with suspected HIT, the HIT-4T score was calculated by treating intensivists using standardized scoring sheets to determine the pretest probability of HIT diagnosis using the following four elements: 1) relative decline in platelet count, 2) time course of platelet decline, 3) presence or absence of thrombosis, and 4) likelihood of another cause for thrombocytopenia (14), with higher scores representing a higher pretest probability. IgG antibody screening against PF4/heparin complexes was performed in all CS patients with suspected HIT. Briefly, screening for anti-PF4/heparin antibodies was performed using the HemosIL AcuStar (Instrumentation Laboratory, Bedford, MA) immunoassay and the ZYMUTEST (HYPHEN BioMED, Neuville-sur-Oise, France) immunoassay (HIA) IgG immunoassay in all patients with suspected HIT. The HemosIL AcuStar HIT-IgG assay is a chemiluminescent two-step immunoassay consisting of magnetic particles coated with PF4 complexed to polyvinyl sulfonate, which capture, if present, PF4/heparin antibodies in a tested sample. Results of HemosIL AcuStar immunoassay greater than or equal to 1.00 U/mL were deemed as potentially indicative of HIT antibodies. ZYMUTEST HIA IgG immunoassay was also performed to detect the presence of anti PF4/heparin IgG antibodies in all patients with suspected HIT. Here, absorbance at 450 nm greater than or equal to 0.30 were deemed as positive. Following positive antibody screening in one or both tests, functional testing was triggered using the heparin-induced platelet activation assay (HIPA) as gold standard in most cases (~95%), the serotonin release assay (SRA), or the platelet aggregation test. Focusing HIPA, washed platelets provided from donors are added to patient serum and heparin, with visual aggregation deemed as a positive result. HIT diagnosis was defined as a positive anti-PF4/heparin IgG antibody test and a positive functional assay result.

CS patients with suspected HIT were subsequently categorized into three groups: anti-PF4 positive (positive anti-PF4/heparin IgG antibodies) (group I), excluded HIT (positive anti-PF4/heparin IgG antibodies and negative functional assay) (group II), and confirmed HIT (positive anti-PF4/heparin IgG antibodies and positive functional assay) (group III). Thus, group I was comprised of all patients in group II and group III. In cases of positive anti-PF4/heparin IgG antibody testing, UFH was stopped and argatroban was initiated according to the medication label as an alternative anticoagulant. All patients were begun on 0.5 μg/kg/min and dose was monitored using aPTT values.

Statistical Analysis

All statistical analyses were performed using R (Version 4.2.2; R Foundation for Statistical Computing, Vienna, Austria). Continuous variables are reported as medians and interquartile ranges (25th–75th). Categorical variables are reported as absolute values and percentages. Characteristics of included patients were

compared using Wilcoxon rank-sum tests for continuous variables. Categorical variables were compared using Fisher exact or chi-square test. All tests were two-tailed, and p values of less than 0.05 were considered significant.

RESULTS

Study Population

In this retrospective dual-center analysis of patients admitted to the cardiac ICU of the university hospital of Munich (LMU) and the university hospital of Bonn between January 2010 and November 2022, a total of 2831 patients with CS were screened. In total, 23 patients were excluded (15 patients due to missing data and eight patients due to known HIT upon admission) from analysis (**Fig. 1**).

HIT Prevalence

In all patients with suspected HIT in this CS cohort, positive anti-PF4/heparin IgG antibodies were found in 159 of 2808 patients (5.7% [4.8–6.5%]). HIT functional testing was subsequently performed in all patients with positive antibody testing. In total, HIT was confirmed following a positive functional assay in 57 of 2808 patients (2.0% [1.5–2.6%]). Thus, in 102 of 2808 patients (3.6% [2.9–4.3%]), the diagnosis could be excluded following a negative functional assay. Last, a PPV of 35.8% and a false positive rate of 64.2% was calculated for the anti-PF4/heparin IgG antibody testing.

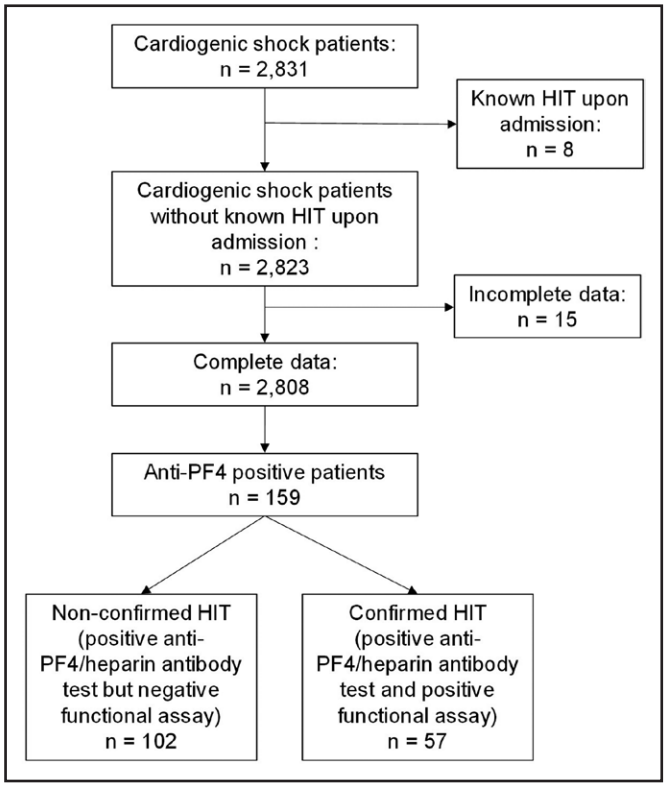

Figure 1. Flow diagram depicting patient selection. HIT = heparin-induced thrombocytopenia, PF4 = platelet factor 4.

Baseline Characteristics and ICU Treatment

Baseline characteristics and data reporting on ICU management are presented in **Table 1** and **Supplementary Table 1** (http://links.lww.com/CCX/B363). Median age of the study population was 65 years and 75.5% of patients were male. History of myocardial infarction was significantly higher in patients with excluded HIT vs. confirmed HIT (25.5% vs. 10.5%; $p = 0.040$), respectively. Nearly half of the study cohort was in Society for Cardiovascular Angiography and Interventions stage E at the time of admission (45.9%). Cardiovascular risk factors were well balanced between groups. Cardiac arrest had occurred in 60 of 159 of the study population (37.7%), with 11 of 159 patients (6.9%) having received extracorporeal cardiopulmonary resuscitation. Cardiomyopathy (32.1%) followed by ST-elevation myocardial infarction (STEMI) (25.2%) and non-STEMI (15.7%) were the most common etiologies leading to CS. No significant difference in the venoarterial ECMO initiation rate (49.0% vs. 36.8%; $p = 0.189$) was observed between excluded and confirmed HIT, respectively. Of the 159 patients (32.7%), 52 required renal replacement therapy and 121 of 159 (76.1%) were mechanically ventilated.

HIT Diagnosis and Management

Median duration of UFH therapy before anti-PF4/heparin IgG antibody testing was 6 days, with no significant difference between patients with excluded and confirmed HIT (d) (6 d [4–11 d] vs. 7 d [4–10 d]; $p = 0.773$), respectively. Further, no significant difference was observed in duration of UFH therapy (d) before HIT functional assay testing between patients with excluded and confirmed HIT (7 d [4–12 d] vs. 8 d [5–10 d]; $p = 0.914$), respectively. HIT-4T-scoring (points) was significantly higher in patients with confirmed than excluded HIT (5 [4–5] vs. 4 [3–5]; $p < 0.001$), respectively. Alternative anticoagulation with argatroban was used following a median UFH therapy of 8 days in patients with confirmed HIT (**Table 2**).

TABLE 1.
Baseline Characteristics and ICU Treatment According to Heparin-Induced Thrombocytopenia Groups

Characteristics	Anti-Platelet Factor 4 Positive Patients (*n* = 159) (I)	Patients With Excluded HIT (*n* = 102) (II)	Patients With Confirmed HIT (*n* = 57) (III)	*p* (II vs. III)
Demographics				
Age (yr), median (IQR)	65 (53–72)	66 (53–73)	63 (54–70)	0.246
Sex (male), *n* (%)	120 (75.5)	72 (70.6)	48 (84.2)	0.095
Body mass index (kg/m²), median (IQR)	27 (24–31)	26 (23–31)	27 (25–30)	0.487
Morbidity at admission				
Simplified Acute Physiology Score II, median (IQR)	66 (55–76)	67 (54–76)	65 (55–77)	0.691
Sequential Organ Failure Assessment, median (IQR)	11 (9–14)	12 (9–13)	11 (8–14)	0.745
Cardiac arrest, *n* (%)	60 (37.7)	38 (37.3)	22 (38.6)	> 0.999
Extracorporeal cardiopulmonary resuscitation, *n* (%)	11 (6.9)	7 (6.9)	4 (7.0)	> 0.999
Society for Cardiovascular Angiography and Interventions at admission, *n* (%)				
A	8 (5.0)	6 (5.9)	2 (3.5)	0.712
B	6 (3.8)	4 (3.9)	2 (3.5)	> 0.999
C	32 (20.1)	20 (19.6)	12 (21.1)	0.991
D	40 (25.2)	25 (24.5)	15 (26.3)	0.951
E	73 (45.9)	47 (46.1)	26 (45.6)	> 0.999
ICU characteristics				
Type of cardiogenic shock, *n* (%)				
ST-elevation myocardial infarction	40 (25.2)	31 (30.4)	9 (15.8)	0.065
Non-ST segment elevation myocardial infarction	25 (15.7)	11 (10.8)	14 (24.6)	**0.039**
Cardiomyopathy	51 (32.1)	33 (32.4)	18 (31.6)	> 0.999
Myocarditis	6 (3.8)	4 (3.9)	2 (3.5)	> 0.999
Cardiac arrhythmia	15 (9.4)	10 (9.8)	5 (8.8)	> 0.999
Pulmonary embolism	5 (3.1)	3 (2.9)	2 (3.5)	> 0.999
Others	20 (12.6)	12 (11.8)	8 (14.0)	0.869

HIT = heparin-induced thrombocytopenia, IQR = interquartile range, *n* = number of patients.
Boldface entry indicates *p* value reaching statistical significance. All *p* values of less than 0.05 were considered statistically significant.

Platelet Counts During CS Treatment

Absolute platelet count values from ICU admission up to day 14 are displayed in Table 2. Maximum platelet count under UFH therapy (g/L) was significantly higher in patients with excluded HIT compared with confirmed HIT (233 [176–303] vs. 181 [148–237]; $p = 0.003$), respectively. By contrast, the minimum platelet count was not significantly different between these groups (58 [39–78] vs. 51 [35–67]; $p = 0.106$). Median absolute change in platelet count is shown in **Table 3**. Both patients with excluded and confirmed HIT showed a significant drop in absolute platelet count over the first 7 days in the ICU (g/L) (–58 g/L [–150 to –4 g/L]; $p < 0.001$ and –74 g/L [–129 to –36 g/L]; $p < 0.001$), respectively. No significant difference in the absolute change in platelet count from baseline was

TABLE 2.
Heparin-Induced Thrombocytopenia Diagnosis and Management

Characteristics	Anti-PF4 Positive Patients (*n* = 159) (I)	Patients With Excluded HIT (*n* = 102) (II)	Patients With Confirmed HIT (*n* = 57) (III)	*p* (II vs. III)
HIT diagnosis				
Continuous unfractionated heparin therapy before HIT suspicion, *n* (%)	159 (100)	102 (100)	57 (100)	
Duration of heparin therapy before anti-PF4/heparin antibody testing (d), median (IQR)	6 (4–10)	6 (4–11)	7 (4–10)	0.773
Positive anti-PF4/heparin antibody testing, *n* (%)	159 (100)	102 (100)	57 (100)	
Duration of heparin therapy before HIT functional assay (d), median (IQR)	7 (4–12)	7 (4–12)	8 (5–10)	0.914
Positive HIT functional assay, *n* (%)	57 (35.8)	0 (0)	57 (100)	
HIT-4T score, median (IQR)	4 (4–5)	4 (3–5)	5 (4–5)	**< 0.001**
HIT management				
Anticoagulant therapy after HIT confirmation				
Argatroban, *n* (%)			57 (100)	
Danaparoid, *n* (%)			0 (0)	
Bivalirudin, *n* (%)			0 (0)	
Duration of heparin therapy before anticoagulation change (d), median (IQR)			8 (6–11)	
Platelet counts				
Platelet count at ICU admission (G/L), median (IQR)	176 (118–233)	185 (115–234)	164 (118–212)	0.556
Platelet count at day 3 after ICU admission (G/L), median (IQR)	101 (70–133)	100 (68–135)	105 (81–131)	0.450
Platelet count at day 7 after ICU admission (G/L), median (IQR)	91 (61–136)	92 (59–141)	88 (64–127)	0.715
Platelet count at day 14 after ICU admission (G/L), median (IQR)	135 (85–242)	151 (87–261)	119 (80–205)	0.218
Minimum platelet count under heparin therapy (G/L), median (IQR)	56 (38–75)	58 (39–78)	51 (35–67)	0.106
Maximum platelet count under heparin therapy (G/L), median (IQR)	208 (161–293)	233 (176–303)	181 (148–237)	**0.003**

HIT = heparin-induced thrombocytopenia, IQR = interquartile range, *n* = number of patients, PF4 = platelet factor 4.
Boldface entries indicate all *p* values reaching statistical significance. All *p* values of less than of 0.05 were considered statistically significant.

found between groups (Table 3). Further, median absolute change in platelet count during ICU stay showed a recovery by day 14 in patients with excluded and confirmed HIT. Plotted platelet counts in patients with excluded and confirmed HIT are provided in **Figure 2**.

Outcomes

Length of ICU stay was significantly longer in patients with confirmed HIT (d) (15 vs. 20; $p = 0.039$), although there was no significant difference in total length of hospital stay (24 vs. 26; $p = 0.277$) between patients with excluded and confirmed HIT, respectively. Total in-hospital mortality (58.8% vs. 57.9%; $p > 0.999$), as well as mortality rates at 1 month (47.1% vs. 43.9%; $p = 0.781$) and 12 months (58.8% vs. 59.6%; $p > 0.999$) were similar between patients with excluded and confirmed HIT, respectively. Further, when stratifying patients by whether they were in the first or last quartile for duration of heparin therapy before anticoagulation change,

TABLE 3.
Time Course of Platelet Counts

		Patients With Excluded HIT ($n = 102$) (I)		Patients With Confirmed HIT ($n = 57$) (II)		
Date 1	Date 2	Median (IQR) of Change in Platelet Count	p for Pairwise Comparison (Date 1 vs. Date 2)	Median (IQR) of Change in Platelet Count	p for Pairwise Comparison (Date 1 vs. Date 2)	p (I vs. II)
ICU admission	Day 3 after ICU admission	−69 (−115 to −27)	**< 0.001**	−59 (−82 to −30)	**< 0.001**	0.171
ICU admission	Day 7 after ICU admission	−58 (−150 to −4)	**< 0.001**	−74 (−129 to −36)	**< 0.001**	0.667
ICU admission	Day 14 after ICU admission	−22 (−92 to 86)	0.392	−57 (−104 to 28)	**0.038**	0.234

HIT = heparin-induced thrombocytopenia, IQR = interquartile range.
Boldface entries indicate all p values reaching statistical significance. All p values of less than 0.05 were considered statistically significant.

no significant difference in in-hospital (57.1% vs. 66.7%; $p = 0.719$), 1-month (42.9% vs. 50.0%; $p = 0.974$), or 12-month mortality (57.1% vs. 66.7%; $p = 0.719$) was observed (**Supplementary Table 2**, http://links.lww.com/CCX/B363). No significant difference in neurologic outcome was found between groups (**Table 4**).

Adverse Events

Bleeding complications were well balanced between groups and represented the most common adverse event during CS treatment. Most patients suffered Bleeding Academic Research Consortium (BARC) 3 bleeding (26.4%) compared with BARC 4 or 5 bleeding (15.7%). No difference in stroke (9.8% vs. 10.5%; $p > 0.999$), hemolysis (12.7% vs. 10.5%; $p = 0.874$), myocardial infarction (1.0% vs. 1.8%; $p > 0.999$), arterial thrombosis (7.8% vs. 10.5%; $p = 0.779$), or venous thrombosis (4.9% vs. 14.0%; $p = 0.067$) was observed between patients with excluded and confirmed HIT, respectively (**Supplementary Table 3**, http://links.lww.com/CCX/B363).

DISCUSSION

In this retrospective dual-center analysis of ICU patients in CS, HIT was confirmed in 2.0 % of the study population, thus representing a rare complication of heparin therapy in this cohort. UFH treatment has been associated with a HIT prevalence of up to 5% in general adult populations, and 1–5% in the critically ill (10, 13, 15–18). HIT was diagnosed in up to 8.3% in several previous analyses including CS patients undergoing venoarterial ECMO (11, 19, 20). Further, the prevalence of HIT among venoarterial ECMO treated patients was 3.4% in a recently published retrospective study conducted at LMU Munich (12). Nearly two of three patients included in our analysis received some form of MCS, a rate higher than in many, particularly older CS cohorts. The rate of MCS deployment has steadily increased over the years. For instance, in Germany, the number of procedures rose from 80 in 2007 to 2614 in 2015, as reported in an analysis of administrative data (21). Treatment with MCS brings certain caveats such as need for continuous anticoagulation, exposure to heparin-coated circuits, high rates of thrombocytopenia, and incomprehensively understood platelet (function, aggregation) alterations. Patients receiving MCS usually require UFH with a target aPTT of at least 60 seconds, whereas not all CS patients, that is, those without indication for therapeutic anticoagulation or interventional procedures, need high doses of UFH. Considering the risk of developing HIT is dependent on cumulative UFH dose, differences in MCS-treated patients compared with general ICU or CS cohorts regarding HIT prevalence may be presumed. However, our study did not include data on UFH indication or exact dose and was thus not specifically designed or powered to address this question. Also, all patients in our cohort treated with venoarterial

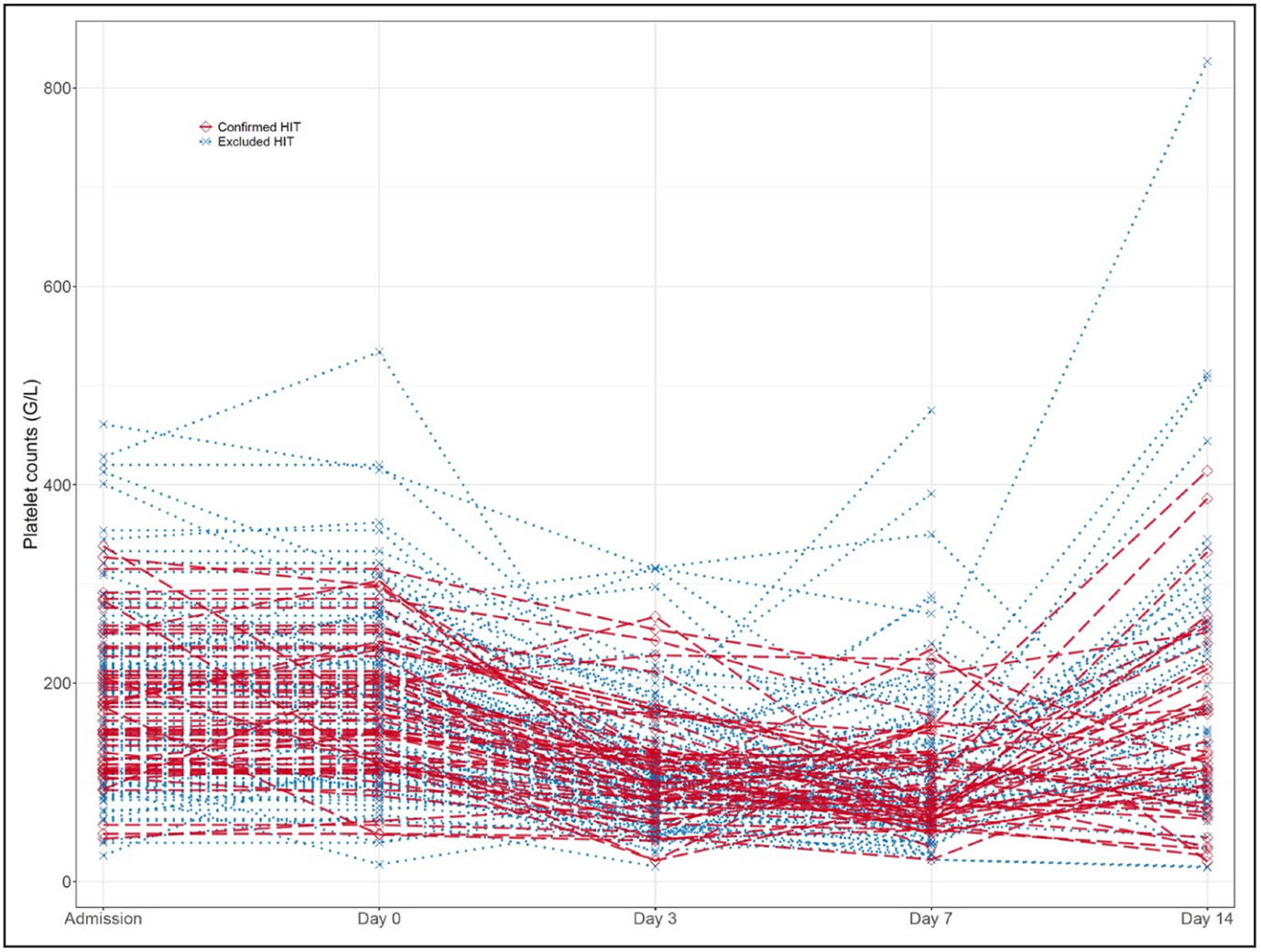

Figure 2. Plotted platelet counts in patients with excluded and confirmed heparin-induced thrombocytopenia (HIT) during ICU stay.

ECMO were exposed to heparin-bonded device circuits, potentially affecting reported HIT prevalence rates as well. With reported rates of thrombocytopenia as high as 23% in venoarterial ECMO patients in one meta-analysis (6), identifying HIT in these patients remains a clinical challenge. Further complicating matters is the potential aggravation of thrombocytopenia due to MCS-induced shear stress from contact with ECMO circuits (22). Interestingly, one systematic review including studies investigating platelet function and aggregation in venoarterial ECMO patients reported that both platelet dysfunction in aggregation as well as reduced expression of platelet adhesion receptors (Glycoprotein Ibalpha and Glycoprotein VI) have been found (6). Further, coagulopathies such as the acquired von Willebrand syndrome, in which high molecular weight von Willebrand factor is lost, have been described in patients with left ventricular assist devices and venoarterial ECMO (23). How these different factors of reduced platelet aggregation, platelet dysfunction, alterations in coagulation, and anticoagulation therapy affect both bleeding and thromboembolic complications remains unclear and will be the subject of future research.

Thrombocytopenia has been reported in 8.3–67.6% of critically ill patients (7, 24). Exclusion of HIT as an underlying cause of thrombocytopenia represents a challenge to intensivists, considering that common prediction models and HIT screening tests have not been validated in ICU patients. In our study, the HIT-4T score was significantly higher in CS patients in whom clinical suspicion of HIT was confirmed by functional testing compared with patients in whom HIT was excluded. Also, maximum platelet counts were significantly lower in the confirmed HIT group. Similar results were seen in venoarterial ECMO

TABLE 4.
Outcome of Cardiogenic Shock Treatment

Characteristics	Patients With HIT Suspicion (*n* = 159) (I)	Patients With Excluded HIT (*n* = 102) (II)	Patients With Confirmed HIT (*n* = 57) (III)	*p* (II vs. III)
Total ICU length of stay (d), median (IQR)	16.01 (9.71–26.00)	14.93 (9.00–23.75)	20.00 (12.00–26.88)	**0.039**
Total hospital length of stay (d), median (IQR)	25.00 (14.75–36.00)	23.50 (12.24–36.00)	26.00 (19.00–35.86)	0.277
Hospital mortality, *n* (%)	93 (58.5)	60 (58.8)	33 (57.9)	> 0.999
1-mo mortality, *n* (%)	73 (45.9)	48 (47.1)	25 (43.9)	0.781
1-yr mortality, *n* (%)	94 (59.1)	60 (58.8)	34 (59.6)	> 0.999
CPC of survivors on hospital discharge, *n* (%)				
CPC 1	14 (8.8)	9 (8.8)	5 (8.8)	> 0.999
CPC 2	15 (9.4)	8 (7.8)	7 (12.3)	0.485
CPC 3	22 (13.8)	15 (14.7)	8 (14.0)	> 0.999
CPC 4	11 (6.9)	7 (6.9)	4 (7.0)	> 0.999

CPC = Cerebral Performance Category, HIT = heparin-induced thrombocytopenia, IQR = interquartile range, *n* = number of patients. Boldface entry indicates all *p* values reaching statistical significance. All *p* values of less than 0.05 were considered statistically significant.

patients, indicating that this finding could relate to HIT pathophysiology in the context of CS (12). By contrast, our dataset does not indicate that absolute change in platelet count is useful in discriminating HIT-induced thrombocytopenia from other etiologies. In cases of clinically suspected HIT, anti-PF4/heparin IgG antibody testing is recommended and is widely being used as part of the standard diagnostic algorithm (25). Although this strategy has yielded a high negative predictive value, the PPV in several CS (sub) population studies has ranged from 8.5% to 53%, with a value of only 35.8% in the present dataset (11, 12, 26, 27). Additionally, adapting the initial HIT screening to specific clinical scenarios, such as CS, to increase pretest probability of antibody screening tests may help to avoid unnecessary and costly functional testing. Our data indicates that an extension of the HIT-4T prediction tool by inclusion of maximum platelet count may improve accuracy and usefulness in clinical practice. This hypothesis needs to be investigated further in independent cohorts.

According to current American Society of Hematology practice guidelines, UFH should be discontinued immediately in patients with intermediate or high clinical probability of HIT (25). Additionally, the guidelines state that argatroban or bivalirudin may be preferred over other non-heparin anticoagulants in critically ill patients due to shorter duration of effect (25, 28, 29). However, there is currently no sound evidence to guide clinical recommendations regarding anticoagulation regimen change in patients with clinically or laboratory suspected HIT. As shown in Table 2, HIT validation turnaround time was fast in our cohort with a median UFH therapy duration of 7 days before anti-PF4/heparin IgG antibody testing, a median UFH therapy of 8 days before functional testing, and argatroban initiation after a median of 8 days following begin of UFH therapy across all patients with confirmed HIT. Patients with confirmed HIT who were switched to argatroban showed sufficient platelet count recovery. Although not a primary aim, many patients with confirmed HIT were treated effectively and safely with this direct thrombin inhibitor in the context of HIT in CS in our study. This result has also been shown in MCS patients (11, 12). Whether basing an anticoagulation regimen change on positive antibody testing, functional testing, or clinical risk prediction alone, influences clinical outcomes is unknown. Considering that in complex cases such as MCS, anticoagulation regimen changes may increase complication risks, this question should be pursued in future studies due to high clinical relevance. Further, future (prospective) trials should address advantages and

disadvantages of argatroban compared with other UFH alternatives such as bivalirudin or fondaparinux in CS, as these drugs have been used successfully to treat HIT (30, 31).

Both HIPA and SRA functional confirmation assays have been described as gold standard tests to confirm the diagnosis of HIT. Both tests are complex, resource intensive, and performed only at specialized laboratories. Few studies have compared diagnostic accuracy of HIPA and SRA in patients with suspected HIT. One small study performed an external quality assessment testing the agreement of the enzyme-linked immunosorbent assay and function assay in six serum samples at seven different laboratories, finding slight discrepancies in SRA and HIPA findings. Potentially limiting preanalytical factors, such as different heparin choices between laboratories for confirmation testing and differences in platelet donors were discussed as potentially impacting agreement of HIPA and SRA test results. Observed higher sensitivity of HIPA compared with SRA may come at the expense of reduced specificity, although this has not been confirmed (32). Further, Selleng et al (33) screened 320 critically ill patients suspected of HIT with anti-PF4/heparin antibodies and performed confirmatory HIPA functional assays. SRA was subsequently performed in all HIPA positive patients. Only strong reactions in the HIPA test were reproducible by SRA and the authors encouraged more stringent definitions of HIPA positive results to avoid overestimation of HIT diagnosis. Despite requirement of radioactive substance to perform testing, the authors argue that measurement of serotonin release from dense granules in the SRA represents a biologically relevant platelet-activating process, while visual assessment of agglutination in the HIPA test does not, potentially explaining higher rates of positive results compared with SRA. Interestingly, one recent study found higher agreement between HIPA and SRA in patients undergoing cardiopulmonary bypass and ECMO than those without (34). Future studies should aim to compare different functional tests and attempt to reduce potentially limiting factors of comparability.

In sum, HIT confirmation was not associated with significant difference in mortality (short- or long-term) or neurologic function among survivors in this study. Similar results have been found in previous analyses that included MCS-treated patients (11, 12). Further, in a retrospective multicenter analysis performed by Kimmoun et al (11), which included 39 venoarterial ECMO patients with a positive HIT screening test, 90-day mortality was 50.0% in patients with subsequently excluded HIT compared with 33.3% in patients with confirmed HIT (p = 0.48). These results indicate that despite lack of high-level evidence, current center-specific diagnostic algorithms and treatment approaches may be effective. Due to low levels of supporting evidence for specific HIT management recommendations in CS and an overall low prevalence of disease, formation of international cooperative networks should be sought to advance our knowledge of pathophysiology and ultimately improve clinical outcomes.

LIMITATIONS

This present analysis is limited by its observational design. This study was conducted at two tertiary centers, thus limiting the generalizability of results. High rates of MCS deployment in our cohort may limit comparability with other studies. Also, differences in diagnostic test reimbursement or alternative anticoagulation regimens between centers, as well as differences in prevalence of HIT between cohorts may influence results, further limiting comparability with previous analyses. Although it is feasible that among all patients meeting CS definition that were screened, there may have been few cases in which clinical suspicion of HIT was not subsequently followed by HIT workup, for example, due to prior death. This limitation to the calculated HIT prevalence would be avoided if HIT were assessed in a prospective trial in CS patients. Further, in our study, we are faced with a situation of verification bias in which disease status is only assessed for patients who screen positive. Consequently, estimates of sensitivity, specificity, and positive and negative likelihood ratios in our cohort would be biased. In this situation, it is generally acknowledged that the only identifiable parameter based on the available data is the PPV. Future studies should include a subset of CS patients who screen negative for anti PF4/heparin IgG antibodies and are tested for HIT using gold standard functional tests to obtain these unbiased values. Additionally, although representing a limitation of our study, lack of standardization in diagnosing HIT reflects real-world practice. Last, although highly specific for the confirmation of suspected HIT, a "limited" sensitivity of functional assays has been described. Thus, some patients who test negatively on functional tests and truly have HIT may be missed.

CONCLUSIONS

In CS patients from two high-volume centers, HIT was a rare complication of UFH therapy occurring in 2.0% of patients and was not associated with increased mortality. Also, HIT confirmation was not associated with worse neurologic outcome in survivors. Patients with confirmed HIT had a significantly higher HIT-4T score and lower maximum platelet count compared with those with excluded HIT, which could potentially increase the accuracy of clinical prediction before laboratory testing. The PPV of anti-PF4/heparin antibody screening tests was 35.8%. Future studies should aim at developing more precise, standardized, and cost-effective strategies to diagnose HIT and prevent complications.

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All ethical standards were met in writing and submitting this correspondence. The study was conducted in accordance with the Declaration of Helsinki and German data protection laws. All data were extracted from the Ludwig-Maximilians University shock registry. The latter is registered at the World Health Organization International Clinical Trials Registry Platform (DRKS00015860) and was approved by the local ethics committee (Institutional Review Board number: 23-0295).

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