**Frequency of thrombocytopenia and heparin induced thrombocytopenia in patients receiving extracorporeal membrane oxygenation compared to cardiopulmonary bypass and the limited sensitivity of pre-test probability score**

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**Abstract**

**Objectives:** To ascertain:

i) the frequency of thrombocytopenia and heparininduced thrombocytopenia (HIT),

ii) positive predictive value (PPV) of the pre-test probability score (PTPS) in identifying HIT

iii) clinical outcome of HIT

in adult patients receiving veno-venous (VV)- extracorporeal membrane oxygenation (ECMO) or veno-arterial (VA)-ECMO, compared to cardiopulmonary bypass (CPB).

**Design**: A single-centre, retrospective, observational cohort study from January 2016 to April 2018

**Setting**: Tertiary referral centre for cardiac and respiratory failure

**Patients:** Patients who received ECMO for >48hrs or had CPB during specified period

**Interventions**: None.

**Measurements and Main Results**: Clinical and laboratory data were collected retrospectively. PTPS and HIT testing results were collected prospectively. Mean age (standard deviation) of the EMCO and CPB cohorts were 45.4 (±15.6) and 64.9 (±13), p< 0.00001. Median duration of CPB was 4.6 [2-16.5] hrs compared to 170.4 [70-1008] hrs on ECMO. Moderate and severe thrombocytopenia were more common in ECMO compared to CPB throughout (p<0.0001). Thrombocytopenia increased in CPB patients on day 2 but was

normal in 83% compared to 42.3 % of ECMO patients at day 10. Patients on ECMO also followed a similar pattern of platelet recovery following cessation of ECMO.

The incidences of HIT in ECMO and CPB were 6.4% (19/298) and 0.6% (18/2998) respectively p<0.0001). There was no difference in prevalence of HIT in patients on VV-ECMO (9/156, 5.7%) vs VA-ECMO (11/142, 7.7%), p=0.81. The PPV of the PTPS in identifying HIT in patients post-CPB and on ECMO were 56.25% (18/32) and 25% (15/60) respectively. Mortality was not different with (6/19, 31.6%) or without (89/279, 32.2%) HIT in patients on ECMO, p=0.79.

**Conclusions**

Thrombocytopenia is already common at ECMO initiation. HIT is more frequent in both VV- and VA-ECMO compared to CPB. PPV of PTPS in identifying HIT was lower in ECMO patients. HIT had no effect on mortality.

**Key Words:** Thrombocytopenia; Extracorporeal membrane oxygenation; cardiopulmonary bypass; heparin induced thrombocytopenia; mortality

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**Introduction**

Thrombocytopenia is common in critically unwell patients (1). It is an independent risk factor for significant bleeding, including intracranial haemorrhage and for a poor outcome in patients receiving Extracorporeal Membrane Oxygenation (ECMO) (2,3). ECMO is a life saving measure for severe respiratory (veno-venous ECMO [VV-ECMO]) or cardiac (veno-arterial ECMO [VA-ECMO]) failure but usually necessitates anticoagulation with unfractionated heparin (UFH), incurring the risk of heparin induced thrombocytopenia (HIT) caused by IgG antibodies formed against the platelet factor 4 (PF4)-heparin complex. These antibody-antigen complexes bind to platelet FcR$\gamma$II receptors causing thrombocytopenia and/or thrombosis (4). The modified cardiopulmonary bypass (CPB) circuit used for ECMO entails exposure to UFH for weeks compared to only a few hours required for CPB. Thrombocytopenia in patients requiring ECMO is multifactorial, thus the accuracy and sensitivity of the 4T pre-test probability score [PTPS] for HIT (degree of **T**hrombocytopenia, **T**ime of onset, presence of new or progressive **T**hrombosis and whether an al**T**ernative cause of thrombocytopenia is likely) may be reduced (5). Modern ECMO circuits have heparin-coated surfaces (6) causing a theoretical risk of continued heparin exposure even if heparin administration is discontinued.

The prevalence of HIT in adult patients receiving VV-ECMO is unknown. The prevalence of HIT among patients under VA-ECMO varies from 0.36% (7) to 8.3% (8). The basic principle of HIT management is to eliminate heparin exposure and to use alternative anticoagulants (5) but practice varies widely. For example, some, but not all, centres switch to non-heparin coated circuits. Argatroban, bivalirudin, fondaparinux and danaparoid have all been used successfully as an alternative anticoagulant (9-12) in HIT but there is no agreed national or international protocol.

Cardiac surgery requiring CPB is also associated with exposure to high doses of UFH, as well as massive platelet activation, a fall-in platelet count and the release of large amounts of PF4 into plasma (13). Up to 50% of CPB patients develop antibodies to PF4-H complexes but <3% of these develop HIT (14-16). At present, the diagnosis of HIT is based on a compatible clinical picture assessed by the 4T PTPS and confirmatory laboratory tests (5;17).

The aims of this study were to ascertain:

i) the frequency of thrombocytopenia and HIT

ii) the positive predictive value (PPV) of the PTPS in identifying HIT

iii) the clinical outcome of HIT

in adult patients receiving VV-ECMO or VA-ECMO, compared to CPB.

**Patients and methods**

This is a retrospective single centre observational cohort study in a tertiary ECMO referral centre in the UK from Jan 2016 to April 2018. The study was approved by the Research Ethics Committee and the local Research and Development Office (Reference number: 19/NW/0474). During the specified period 340 patients received ECMO. Patients who received ECMO for ≤48hrs or did not receive heparin at initiation of ECMO were excluded from the study. A total of 298 patients ≥16 years old (156 VV-ECMO, 142 VA-ECMO) met the study criteria and were included for analysis (Figure 1). A total of 2998 patients who had CPB during the study period formed the comparator group.

***ECMO and anticoagulation***

VV-ECMO is mainly peripheral and VA-ECMO is peripheral or central. We use Heparin sodium 20,000units/20ml solution (Fannin (UK) Ltd) or Heparin sodium 10,000units/10ml

solution (Wockhardt UK Ltd) without preservative. A heparin bolus dose is given at cannulation, followed by heparin infusion during ECMO as previously described (2). The target heparin anti-Xa concentration was 0.2-0.3 units/ml for VV-ECMO and 0.3-0.5 units/mL for VA-ECMO.

***Data collection and control group***

Demographic, radiological, laboratory and clinical data were extracted from the clinical Data Warehouse and patient electronic records. PTPS were collected from the Trust HIT screen request form (supplemental document 1). All patients had at least one platelet count per 24hrs: when ECMO patients had >1 count per day, the average was taken.

**Laboratory testing for HIT**

An initial HIT antibody screen was performed on an ACL TOP500 analyser using the Hemosil HIT-Ab (PF4-H) kit (Werfen UK); a rapid qualitative, fully automated, latex immunoturbidometric assay (LIA). The assay is interpreted as either positive or negative according to the manufacturer's recommendation wherein a "positive" assay result is >1.0 U/mL. If positive, a confirmatory ELISA assay (HYPHEN BioMed, Neuville-sur-Oise, France) was performed for which an optical density (OD) of >0.5 is considered positive according to the manufacturer's guidance. Given the relatively low specificity and positive predictive values of the ELISA test, if the ELISA OD value was 0.5-0.9, the sample was further tested using the Hemosil® AcuStar HIT-IgG (PF4-H) which is an automated chemiluminescent immunoassay. For this third assay the manufacturer recommends that a result of ≥1.00 U/mL should be considered positive. If the Hemosil® AcuStar HIT-IgG (PF4-H) was also positive, a diagnosis of HIT was made. Finally, patients with low PTPS (3) but a positive

screening test and ELISA were also tested using the Hemosil® AcuStar HIT-IgG (PF4-H). In these patients, if all three tests were positive, they were diagnosed as HIT (Figure 1). Patient with intermediate or high PTPS score, positive LIA and ELISA OD value of ≥ 1.0 considered as positive for HIT without performing Hemosil® AcuStar HIT-IgG (PF4-H).

***Heparin induced thrombocytopenia***

Patients with a history of HIT were excluded from the study. If patients had been exposed to heparin prior to ECMO or CBP then this was taken into account in calculating the 4T score. None of these patients had positive HIT results during the study period. Otherwise, screening for HIT was performed in patients who developed thrombocytopenia in a pattern suggestive of HIT, with or without objectively proven thrombosis. Suspected cases were discussed with a consultant haematologist to arrange testing and anticoagulation. PTPS was calculated by two clinicians (requesting clinician and on-call haematologist) and the form was completed by the requesting clinician. If the PTPS score was high (6-8), heparin was stopped and an alternative anticoagulant started pending laboratory tests. If the score was intermediate (4-5), a HIT screen was performed and only patients with positive screen results were switched to alternative anticoagulant. Patients with low PTPS (<4) were not tested except for a selected group with a score of 3 but in whom alternative causes were discounted by the clinicians. All patients with positive screen results were switched to argatroban until a second confirmatory test (an ELISA performed on the original sample) result was available (<24hrs). Those confirmed positive by ELISA, continued to receive argatroban. Those with negative ELISA or OD value of 0.5-0.9 or patients with low PTPS but positive screen test with LIA and ELISA were further tested with the AcuStar immunoassay detailed above. If this result was also negative, the patient was switched back to UFH.

**Management of HIT**

All patients with HIT switched to argatroban 0.2 microgram/kg/min, subsequently adjusted to achieve an APTT of 47 – 78 (normal range 26-36) seconds.

***Thrombotic events (definition and the diagnosis)***

Thrombosis was defined as objectively confirmed vascular occlusion of venous or arterial circulation or visible occlusion of the ECMO circuit or sudden large rise in D dimer levels (doubling in value within 72hrs) in the absence of other explaining pathology in combination (18) with a noisy pump indicative of pump head thrombosis requiring a change of circuit. Diagnosis of Venous thromboembolism (VTE) was performed by duplex ultrasound scan (USS), CT scan or magnetic resonance angiography. Doppler USS of the lower limbs was performed routinely in all patients who had a femoral cannula at the time of removal. Other scans were only performed when clinically indicated. Thromboembolic events up to 3 days after decannulation or ECMO circuit clotting events necessitating emergent oxygenator exchange were included (7).

**Bleeding events**

Bleeding was defined according to ISTH SSC criteria for major and minor bleeding (19).

**Statistical analysis**

Data analysis was performed using Stata version 14 and GraphPad Prism® version 8 (GraphPad Software, Inc. La Jolla, USA). Categorical data were compared using the chi-squared or Fishers exact test. Numeric data were tested for normality using Shapiro-Wilk test. Two sample independent t-tests were used to compare normally distributed numeric

data between groups, while the Wilcoxon rank-sum (Mann-Whitney) test was used for non-normal data. All statistical tests were 2 sided and significance was set at $p < 0.05$.

## Results

### *Population characteristics and thrombocytopenia*

CPB patients were older than ECMO patients; mean age (± standard deviation) 64.9 (±13) vs 45.4 (±15.6), p< 0.0001. A significantly higher proportion of CPB (71.3%) and ECMO (58.5%) patients were male, p<0.0001. Median duration on CPB was 4.6 [2-16.5] hrs compared to 170.4 [70-1008] hrs on ECMO, p<0.0001.

Thrombocytopenia was divided into mild (100-150x$10^9$/L), moderate (50-99x$10^9$/L) and severe (<50x$10^9$/L) (Table 1 and Figure 2A). The incidences of severe thrombocytopenia and moderate thrombocytopenia were 4.4% and 40% respectively at the initiation of ECMO which was significantly higher than in CPB patients (p<0.0001) and this difference remained significant on days 2, 5 and 10. Patients on CPB typically suffered a fall in platelet count by day 2-5 and almost 83% recovered their platelet count to normal by day 10 whilst the platelet count remained low in patients on ECMO. However, these patients gradually recovered their platelet count following cessation of ECMO (post ECMO). Patients on either VA-ECMO (Table 2A and Figure 2B) or VV-ECMO (Table 2B and figure 2C) showed a similar pattern of platelet recovery post ECMO but only around 70% of the patients on VA-ECMO had normal platelet count by day 10 compared to 83% in patients on CPB and VV-ECMO.

### *Diagnosis of HIT*

A total of 95 patients had HIT screening tests (63/298, 21.1% of patients on ECMO [VV-ECMO=27, VA-ECMO=36) and 32/2988, 1.1% patients who received CPB). Screening was

positive in 21 patients (21/298, 7.0%) on ECMO and 19 (18/2998, 0.63%) on CPB (p<0.0001) Figure 1. Nineteen out of 21 patients with positive HIT screen test on ECMO had positive results with ELISA (19/21, 90.5% PPV of the screen test) and 18/19 patients on CPB (94.7% PPV) (Figure 1). Therefore, the incidences of HIT in ECMO and CPB patients were 6.4% (19/298) and 0.6% (18/2998) respectively<0.0001). There was no difference in the incidence of HIT in patients on VV-ECMO (8/156, 5.1%) vs VA-ECMO (11/142, 7.7%), p=0.47 (Figure 1, supplemental table 1 and 2). Median PTPS of patients with HIT was 4 (3-7) on ECMO compared to 5 (4-7) post CPB, p=0.039 (supplemental Figure 1). PPV of the PTPS (using a cut-off 4) in identifying HIT in patients post CPB and on ECMO were 56.25% (18/32) and 25% (15/60) respectively.

Three patients on ECMO with PTPS of 3 were tested for HIT despite not being recommended by current guidelines (5). Clinical details of these three patients are given in Table 4. All three patients were on renal replacement therapy and on medications that can cause thrombocytopenia. However, they all had a typical pattern of platelet fall following the start of UFH and ECMO and all developed thrombosis which prompted the screening for HIT despite the low PTPS. All three patients had high OD values with ELISA (≥ 1.5) and positive results with Hemosil® AcuStar HIT-IgG (>2.0).

Median (range) OD with ELISA for patients on ECMO and CPB were 2.0 (0.7-3.5) and 2.0 (0.8-3.6) respectively (p=0.8). There was no difference in the PTPS in patients with suspected HIT on ECMO whether HIT screen test was positive or negative confirming the poor PPV of PTPS in this group.

***Thrombosis and Bleeding events in patients with and without HIT on ECMO***

Major bleeding occurred in one patient with HIT (1/8, 12.5%) on VV-ECMO. This was a 61-year-old male with severe Pneumococcal pneumonia. At the initiation of ECMO, his platelet was 214 x109/L and fell to a nadir of $61x10^9$/L within 8 days of commencing ECMO. His PTPS was 5 and had positive HIT screening with LIA and an OD value of 3.1 by ELISA. He developed multi-organ dysfunction with severe liver failure and deranged coagulation factors including very low fibrinogen. He was not anticoagulated due to bleeding. CT scan revealed bilateral pulmonary emboli, extensive thrombosis in abdominal vessels and splenic and liver infarcts. The patient died within 48hrs patients of diagnosis of HIT. Because his platelet count was >50 x109/L and he had deranged coagulation factors and abnormal thromboelastograpy with prolonged R time and reduced functional fibrinogen, bleeding was not a direct consequence of thrombocytopenia or due to anticoagulation. None of the patients with HIT following CPB or VA-ECMO had major bleeding. Overall major bleeding rates in VA-ECMO and VV-ECMO were 27.5% (39/142) and 23.7% (37/156) respectively and was higher in patients without HIT p=0.03. Overall thrombosis rates in patients who received VA-ECMO and VV-ECMO were 21.1% (30/142) and 27.5% (43/156) respectively and patients confirmed to have HIT had significantly higher rates of thrombosis compared to those without HIT, P<0.0001. However, there was no difference in the median (range) time on ECMO to development thrombosis in HIT patients (7 days [5-11]) vs patients without HIT (12 days [3-65]), p=0.98.

***Thrombotic events and platelet recovery in patients with HIT on ECMO vs CPB***

Thrombotic events occurred in 89.5% (17/19) of HIT patients on ECMO compared to 55.5% (10/18) of patients with HIT post CPB, p=0.029. Characteristics of HIT patients are shown in supplemental tables 1 and 2 respectively. Therefore, the incidence of HIT with thrombosis

(HITT) in patients on ECMO and CPB were 5.74% (17/296) and 0.33% (10/2998) respectively. During ECMO, median time to platelet recovery of >50% above the nadir after switching to argatroban was 96hrs (48-120) in ECMO vs 72 hrs (24-96) in CPB, p=0.04. HIT-negative ECMO patients recovered their platelet count to >50% above nadir in a median of 144hrs (96-288), p<0.0001 compared to 48 hours for CPB (24-96).

***30-day mortality in patients receiving ECMO***

Overall 30-day mortality was 31.9% (95/298) in ECMO patients (VA-ECMO= 37.3% [53/142] and VV-ECMO= 26.9% [42/156]). There was no difference in the mortality rate in patients with or without HIT (89/279, 32.2% v 6/19, 31.6%), p =0.79 in the overall group or on VV-ECMO (2/8, 25% vs 40/148, 27.0%, p=0.89) or VA-ECMO (4/11, 36.4% vs 49/131, 37.4%, p=0.94). No difference was observed in the mortality rate in patients on ECMO with HIT (1/2, 50% vs HITT (5/17, 29.4%), p=0.96.

**Discussion**

We report the single centre incidence of thrombocytopenia and HIT/HITT in a large cohort of patients receiving ECMO compared to patients undergoing CPB. The most important findings from this study are that HITT is significantly more common in patients on ECMO than CPB and the possibility of HITT should be considered and promptly investigated even in the presence of a low PTPS. Patients on ECMO and CPB showed distinct patterns of thrombocytopenia which will be useful in assessment of this risk. Patients having CPB typically showed a fall in platelets by day 2-5 and 83% recovered to normal by day 10. Thrombocytopenia was significantly more common at day 1 in ECMO patients and remained

low until it was discontinued. However, following cessation of ECMO, these patients had similar pattern of platelet recovery to patients on CPB.

Thrombocytopenia in critically ill and ECMO patients is multifactorial. Likely contributing factors are infections, haemodilution, drugs, disseminated intravascular coagulation and exposure to the ECMO circuit surface (1). Our observed frequency of thrombocytopenia is similar to other studies in critical care patients (20). Unlike CPB patients, the majority of ECMO patients remained thrombocytopenic at day 5 and 10 which is the peak period for development of HIT after exposure to UFH making it difficult to calculate the PTPS. Consequently, compared to a 56.25% PPV of the PTPS in identifying HIT in post-CPB patients, it was only 25% in patients receiving ECMO. This is important because the incidence of HIT in patients on ECMO was 6.4% compared to 0.6% in CPB patients. The value of PTPS in identifying HIT in patients on ECMO has not previously been studied but our results are consistent with those in other critically ill patients (21).

We diagnosed HIT in three patients (15.8%) with a PTPS of 3 who would not usually merit further investigation (5;17) suggesting that reliance on the PTPS could result in a significant number of HIT cases being missed.

In a retrospective cohort study of 96 patients on VA-ECMO, Sokolovic et al reported HIT and HITT in 8.3% and 7.3% of patients respectively (8). Only 4 patients had functional testing by serotonin release assay (SRA), three were not tested with SRA and one patient with negative SRA but positive ELISA was considered to have HITT. Two patients considered negative by ELISA had positive SRA results. Our results for VA-ECMO patients (6.4% and 5.7%) are similar to Sokolovic et al (8) but we also show that the incidence is similar in VV-ECMO patients [5.8% (9/156) 5.1% (8/156)]. In contrast, another retrospective study found an

extremely low incidence of HIT in VA-ECMO (0.36%) (7). However, in this study 14/39 patients (36%) with a positive immunoassay were excluded as HIT following a negative functional assay. Despite this, 71.4% of those thought not to have HIT were switched to argatroban compared to 52.4% of those with confirmed HIT.

The time to platelet recovery of at least 50% above platelet nadir was significantly shorter in patients with confirmed HIT after switching to argatroban compared to those with negative HIT suggesting different aetiologies. However, patients with HIT on ECMO took a longer time to reach a platelet count >50% above the nadir compared to patients who had had CPB, probably due to the effect of the ECMO circuit and on-going additional factors for thrombocytopenia. Three patients with low PTPS (3) had a positive HIT screen confirmed by two different immunoassays. We did not perform a functional assay, such as the serotonin release assay (SRA) which is considered the gold standard test for confirming HIT. This was not available in the laboratory serving the hospital. Introducing radioactive methods into a diagnostic service laboratory is a difficult and cumbersome exercise which is not practical within existing budgets. Currently SRA is not available in UK laboratories. However, with increase in platelets within 96hrs of switching to argatroban without thrombosis or bleeding supports the diagnosis of HIT/HITT. Whilst there are there are no studies comparing efficacy of argatroban in patients with HIT/HITT to those with thrombocytopenia due to other causes, patients with HITT treated with argartroban achieved significantly more rapid rise in platelet counts compared with those in historical controls (22). The LIA test used for HIT screening our study has shown a sensitivity of 97.4% and specificity of 94.0% in a prospective study using the SRA test (23). In a systematic review and meta-analysis of diagnostic value of immunoassays for diagnosis of HIT, a combination of high sensitivity

(>95%) and specificity (>90%) was observed with CLIA. However, with ELISA, high sensitivity (99.6%) but relatively low specificity (89.9%) was observed compared to SRA (24). According to both British Society for Haematology (5) and American Society of Haematology guidelines (17), a PTPS of ≥ 4 with positive immunoassay is sufficient to make the diagnosis of HIT.

In our study only 21.6% of the patients on ECMO had HIT screening compared to 74% in the study by Sokolovic et al (8) but the incidence of HIT/HITT was similar in two studies. Our lower screening and higher positivity rates may reflect discussion with a consultant haematologist on call.

None of the previously discussed studies or this study found a difference in the hospital mortality for patients with HIT compared to those without (13,14). This is probably due to prompt recognition and switching to a non-heparin alternative anticoagulant in most of the patients.

The higher prevalence of HIT in patients on ECMO (VA-ECMO or VV-ECMO) compared to CPB patients in our study could be multifactorial. For the pathogenesis of HIT, stoichiometrically optimal PF4-to-heparin ratios are needed. A stoichiometry-based model has shown that optimal heparin/PF4 complex formation occurs at prophylactic- UFH dose and high PF4 levels (25). Patients undergoing CPB receive a very high dose of UFH and release of a large amount of PF4 into the circulation; after the bypass protamine is used to reverse the heparin effect. Subsequently, most patients do not require further UFH unless there is mechanical heart valve and many patients continue low molecular weight heparin (LMWH) at either prophylactic or treatment dose which carries a much lower risk of HIT. In contrast, ECMO patients receive a bolus dose of heparin at the time of cannulation (usually

20-25units/kg with maximum 5000units) followed by systemic UFH to maintain heparin anti-Xa levels of 0.2-0.3 for VV-ECMO and 0.3-0.5 for VA-ECMO. Therefore, EMCO patients are more likely to achieve stoichiometrically optimal PF4-to-heparin ratios than patients undergoing CPB. In addition, patients on ECMO have on-going infection/inflammation that can further increase the risk of immunisation with heparin/PF4 complexes.

The role of heparin coated ECMO circuit in HIT is uncertain (26) but it is unlikely that it diffuses into the blood. Koster et al, did not find any enhancement of heparin-PF4-IgG complex-associated immunologic or thrombogenic reactions when using a heparin-coated system(27). Most cases reports, cohort studies (28-30) and our cohort, showed good recovery of platelet without changing the circuit.

The lack of a functional assay to confirm HIT/HITT is the main limitation in this study. As the study is single centre, results may not applicable to all centres due to differences in practice such as position of ECMO cannula, circuits, heparin formulation and dosing as these may affect the stoichiometry of heparin/PF4 complex formation.

Despite the above limitations, this study has many strengths: it the largest single centre study to date reporting the incidence of thrombocytopenia and HITT/HITT in patients receiving VV-ECMO or VA-ECMO compared to patients received CPB and all patients were managed uniformly. All relevant clinical information and laboratory data were available to assess the study outcomes. Furthermore PTPS, HIT testing, results and management of HIT/HITT and the clinical outcomes were collected prospectively.

**Conclusions**

Thrombocytopenia is a common feature at ECMO initiation. CPB patients showed an early fall in their platelet count but generally recovered by day 10. Patients on ECMO also followed a similar pattern of platelet recovery following cessation of ECMO, although patients on VA-ECMO showed a slightly longer time to recover the platelet count compared to others. HIT is more frequent in both VV- and VA-ECMO compared to CPB. Although PTPS was useful in predicting HIT in patients on CPB, it was less reliable in patients on ECMO, and it failed to detect HIT in 15.8% ECMO patients. HIT had no effect on mortality in patients on ECMO. Patients on ECMO showed good recovery of platelet after switching to argatroban without changing the circuit to non-heparin bonded alternative. Low PTPS does not reliably exclude HIT/HITT in patients on ECMO and those with a decline in platelet count suggestive of HIT/HITT should be promptly investigated even if the PTPS is low.

**Author contributions**

D. R.J. Arachchillage was responsible for design of the study, acquiring data, some of the statistical analysis, interpretation of the data and writing the first draft of the manuscript. M. Laffan, S Ledot, and B Patel critically evaluated the manuscript. S Khanna, C. Vandenbriele, F Kamani, M Passariello, A Rosenberg, TC Aw, A Rosenberg and S Ledot collected the data. W Banya performed statistically analysis. All authors commented and approved the final manuscript.

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**Disclosure of conflict of interest**

Authors indicated no potential conflicts of interest.

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**Legends to figures**

**Figure 1.** Flow diagram showing diagnosis of heparin induced thrombocytopenia in patients on veno-venous extracorporeal membrane oxygenation (VV-ECMO) and veno-arterial ECMO (VA-ECMO).

Figure 2. Platelet counts over time in patients had cardiopulmonary bypass (CPB) [2A], veno-arterial (VA) extracorporeal membrane oxygenation (ECMO) [2B] and veno-venous ECMO (VV-ECMO) [2C]. Bars indicate mean and standard deviation of the platelet count of the relevant days. As the median duration from pre-CPB to end of CPB was 4.6 [2-16.5] hrs compared to 170.4 [70-1008] hrs from pre-ECMO to end of ECMO, these time points are shown as dotted lines.

**Figure 1**

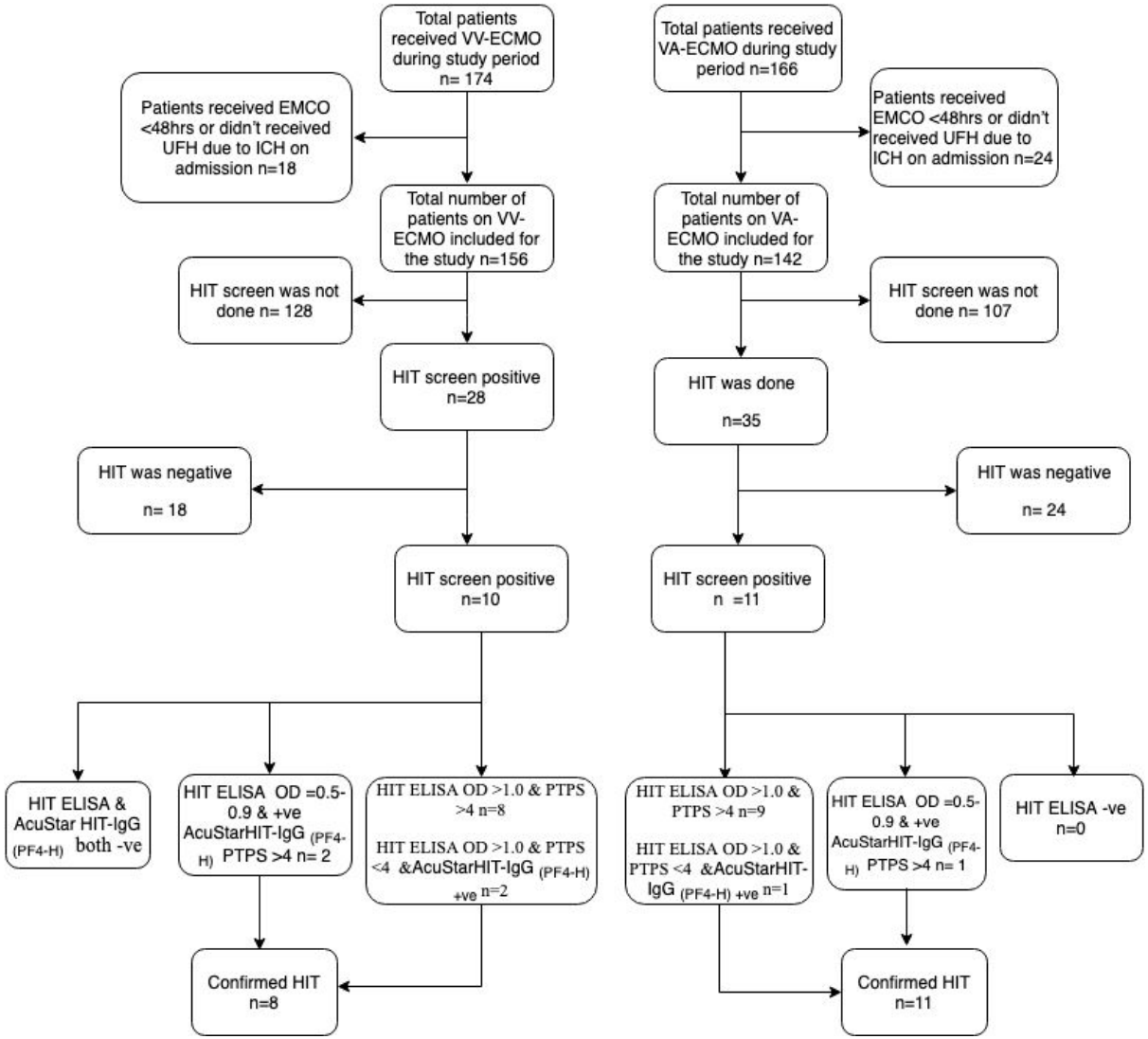

Total patients received VV-ECMO during study period n= 174
Patients received EMCO <48hrs or didn't received UFH due to ICH on admission n=18
Total number of patients on VV-ECMO included for the study n=156
HIT screen was not done n= 128
HIT screen positive n=28
HIT was negative n= 18
HIT screen positive n=10
HIT ELISA & AcuStar HIT-IgG (PF4-H) both -ve
HIT ELISA OD =0.5-0.9 & +ve AcuStarHIT-IgG (PF4-H) PTPS >4 n= 2
HIT ELISA OD >1.0 & PTPS >4 n=8
HIT ELISA OD >1.0 & PTPS <4 &AcuStarHIT-IgG (PF4-H) +ve n=2
Confirmed HIT n=8
Total patients received VA-ECMO during study period n=166
Patients received EMCO <48hrs or didn't received UFH due to ICH on admission n=24
Total number of patients on VA-ECMO included for the study n=142
HIT screen was not done n= 107
HIT was done n=35
HIT was negative n= 24
HIT screen positive n =11
HIT ELISA OD >1.0 & PTPS >4 n=9
HIT ELISA OD >1.0 & PTPS <4 &AcuStarHIT-IgG (PF4-H) +ve n=1
HIT ELISA OD =0.5-0.9 & +ve AcuStarHIT-IgG (PF4-H) PTPS >4 n= 1
HIT ELISA -ve n=0
Confirmed HIT n=11

**Figure 2**

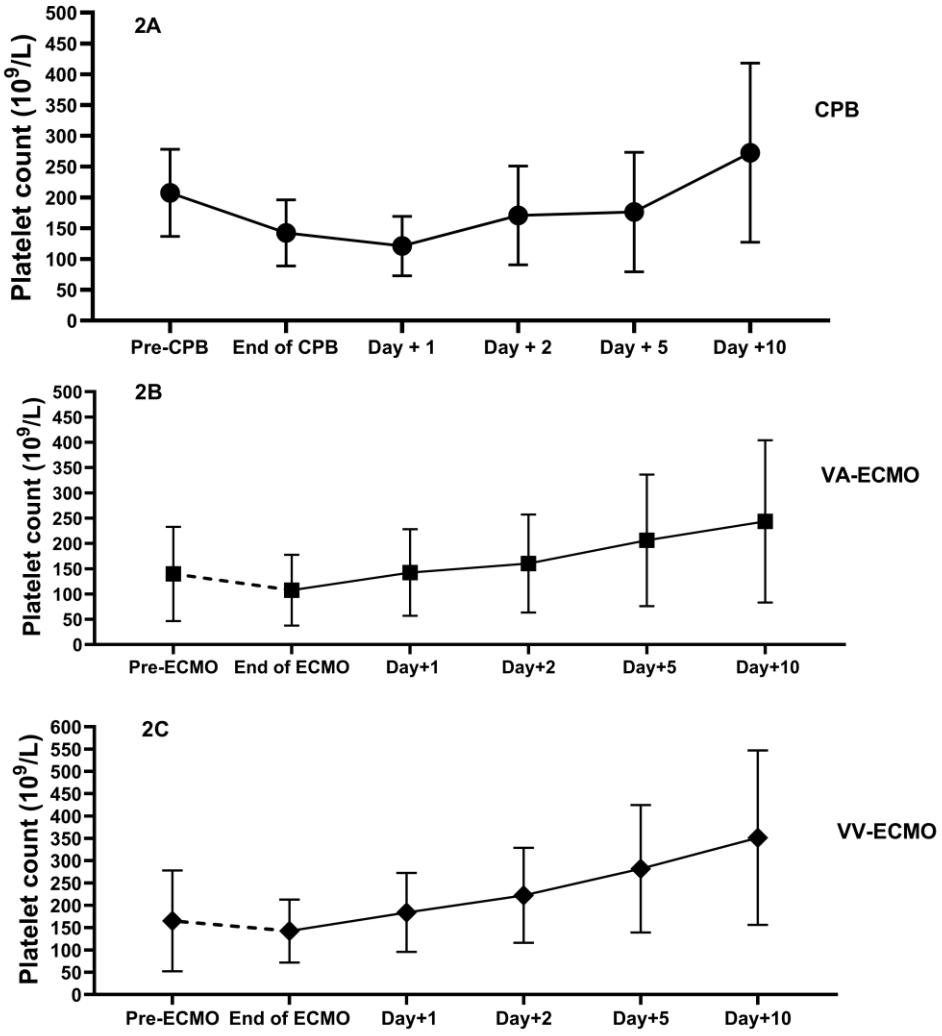

2A
Platelet count ($10^9$/L)
500
450
400
350
300
250
200
150
100
50
0
CPB
Pre-CPB
End of CPB
Day + 1
Day + 2
Day + 5
Day +10
2B
Platelet count ($10^9$/L)
VA-ECMO
Pre-ECMO
End of ECMO
Day+1
Day+2
Day+5
Day+10
2C
Platelet count ($10^9$/L)
600
550
VV-ECMO
Pre-ECMO
End of ECMO
Day+1
Day+2
Day+5
Day+10

**Table 1. Proportions of patients undergoing extracorporeal membrane oxygenation or cardiopulmonary bypass with different degrees of thrombocytopenia on days 1, 2, 5 and 10**

| **Degree of thrombocytopenia** | | **Severe (<50x109/L) %** | **Moderate (50-99x109/L) %** | **Mild(100-150x109/L) %** | **Normal platelet >150x109/L %** |
|---|---|---|---|---|---|
| Day 1 | CPB | 0.2 | 14.5 | 50 | 35.36 |
| | ECMO | 4.4 | 40.0 | 23.2 | 32.4 |
| Day 2 | CPB | 0.9 | 32.4 | 46.8 | 19.8 |
| | ECMO | 4.1 | 51.3 | 21.0 | 23.6 |
| Day 5 | CPB | 2.0 | 14.0 | 23.6 | 60.5 |
| | ECMO | 9.4 | 46.3 | 22.5 | 21.7 |
| Day 10 | CPB | 1.6 | 6.3 | 9.4 | 82.7 |
| | ECMO | 4.1 | 26.0 | 27.6 | 42.3 |

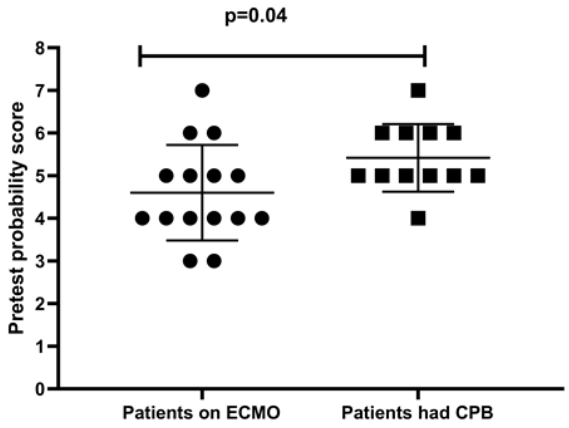
CPB= cardiopulmonary bypass, ECMO= Extracorporeal membrane oxygenation

**Table 2: Proportions of patients with different degrees of thrombocytopenia post VA ECMO (2A) and post VV-ECMO (2B)**

| Degree of thrombocytopenia | Severe (<50 x 109/L) % | Moderate (50-99 x 109/L) % | Mild (100-150 x 109/L) % | Normal platelet >150 x 109/L % |
|---|---|---|---|---|
| **VA-ECMO (2A)** | | | | |
| Day 0 (day of decannulation) | 4.1 | 50.7 | 30.2 | 15 |
| Day 1 | 2.46 | 45.08 | 27.87 | 24.59 |
| Day 2 | 4.27 | 35.04 | 28.21 | 32.48 |
| Day 5 | 2.78 | 19.44 | 19.44 | 58.33 |
| Day 10 | 2.15 | 13.98 | 13.98 | 69.89 |
| **VV-ECMO (2B)** | | | | |
| Day 0 (day of decannulation) | 3.1 | 29.2 | 47.2 | 20.5 |

| | | | | |
|---|---|---|---|---|
| Day 1 | 2.44 | 21.14 | 43.09 | 33.33 |
| Day 2 | 1.65 | 15.70 | 22.31 | 60.33 |
| Day 5 | 1.27 | 11.39 | 6.33 | 81.01 |
| Day 10 | 0 | 6.90 | 10.34 | 82.76 |

**Supplemental Figure 1**



**Supplemental document 1. Heparin Induced Thrombocytopenia (HIT) Request Form**

| | | |
|---|---|---|
| Patient<br><br>Name: | PLEASE SEEK ADVICE FROM CONSULTANT HAEMATOLOGIST IN ALL CASES OF SUSPECTED HIT REGARDLESS OF THE ALGORITHM SCORE** | Requesting<br><br>Dr: |
| Hospital<br><br>Number: | | Bleep: |
| Date of<br><br>Birth: | | Consultant: |
| Ward: | | Date: |

- Patient diagnosis: Indication for heparin:
- Heparin type and dose Date commenced:
- Date of most recent dose
- Previous heparin exposure (in last 100/7): Y/N
- Platelet count pre- heparin (x$10^9$/L)..... Platelet nadir post heparin(x$10^9$/L)..... Date

**Pre-test algorithm:**

| **Thrombocytopenia** | **Score** | **Tick** |
|---|---|---|
| <30% fall or platelet count 10-19 x $10^9$/L | **0** | |

Refer to guidelines on intranet for more

**Low Score (0 -3)**

- Continue to monitor platelet count

| | | |
|---|---|---|
| 30-50% fall or platelet count 20-100 x$10^9$/L | **1** | |
| >50% fall and platelet count 20-100 x $10^9$/L | **2** | |
| **Timing of Thrombocytopenia** | | |
| <5d with no previous heparin exposure | **0** | |
| Possibly d 5-10 but unclear | **1** | |
| D 5-10 or less if previous heparin exposure in past 100 days | **2** | |
| **Thrombosis** | | |
| None | **0** | |
| Progressive or recurrent thrombosis or skin lesions or suspected but unproven new thrombosis | **1** | |
| New thrombosis, skin necrosis, acute systemic reaction following heparin injection | **2** | |
| **Other causes of thrombocytopenia** | | |
| Definite other cause | **0** | |
| Possible other cause | **1** | |
| No other cause | **2** | |

information

**Total Score**

.....

See also BCSH guidelines:

- Treat alternative cause

**Intermediate score (4-5)**

- Stop heparin
- Discuss further management with Haem Consultant**
- Send sample with this form for HIT screen ( 1 citrate (blue top) sample)

**High score (6-8)**

- Stop heparin
- Discuss further management with Haem Consultant**
- Send sample with this form for HIT screen ( 1 citrate (blue top) sample)
- Commence full dose alternative anticoagulant

**Table 3: Clinical and laboratory characteristics of three patients with low pre-test probability score and diagnosed to have heparin induced thrombocytopenia.**

| **Patient and age** | **Indication for ECMO and type of ECMO** | **Platelet count at the initiation of ECMO and (Platelet nadir) (109/L)** | **% decrease in platelet count at the diagnosis of HIT)** | **Duration in EMCO at the diagnosis of HIT (days)** | **HIT ELISA OD value and (Hemosil® AcuStar HIT-IgG value)** | **Cause of thrombocytopenia other than HIT, being on ECMO and severe sepsis** | **Thrombotic event** |
|---|---|---|---|---|---|---|---|
| 1<br>38years | Myocarditis<br>VA-ECMO | 121 (19) | 79 | 11 | 1.5 (3.5) | Diuretics, Beta blockers, renal replacement therapy | Left femoral artery thrombosis and ECMO cannula site thrombosis |
| 2<br>40 years | Staphylococcus aureus bilateral pneumonia<br>VV-ECMO | 80(19) | 76 | 5 | 2.4 (3.0) | Clindamycin, ciprofloxacin, PPI, renal replacement therapy | Partial thrombosis of the common femoral vein |
| 3<br>48 years | Viral pneumonia<br>VV-ECMO | 90 (18) | 78 | 9 | 2.5 (2.8) | PPI, renal replacement therapy, Anti-viral treatment | left internal jugular vein thrombosis |

ECMO= extracorporeal membrane oxygenation; VA= veno arterial; VV= veno venous; HIT= heparin induced thrombocytopenia; B/L= bilateral; * samples were tested with alternative immunoassay with Hemosil® AcuStar HIT-IgG (PF4-H) and results were positive for both patients, proton pump-inhibitors

**Supplemental Table 1: Characteristics of patients diagnosed as heparin induced thrombocytopenia on veno-venous extracorporeal membrane oxygenation**

| Patient | Age Year | sex | Indication for ECMO | Platelet count at the initiation of ECMO (109/L) | Platelet nadir(109/L) | % decrease in platelet count at the diagnosis of HIT | Duration in EMCO at the diagnosis of HIT (days) | HIT ELISA OD value | PTPS | Cause of thrombocytopenia other than HIT, being on ECMO and severe sepsis | Thrombotic event | 30-day outcome |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 56 | M | Pneumococcal pneumonia | 185 | 51 | 72 | 6 | 0.9* | 4 | Ceftriaxone, PPI, renal replacement therapy | B/L PE | alive |
| 2 | 54 | F | B/L Pneumonia, H1N1 positive | 200 | 60 | 70 | 5 | 2.5 | 4 | Anti-viral treatment, PPI | No thrombosis | alive |
| 3 | 48 | F | Viral pneumonia | 90 | 18 | 78 | 9 | 2.5 | 3 | PPI, renal replacement therapy, Anti-viral treatment | left internal jugular vein thrombosis | alive |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 4 | 45 | M | Influenza A and pneumococcal pneumonia | 112 | 49 | 56 | 7 | 2.6 | 4 | Anti-viral treatment, PPI, cefuroxime, | No thrombosis | dead |
| 5 | 40 | F | Staphylococcus aureus bilateral pneumonia | 80 | 19 | 76 | 5 | 2.4 | 3 | Clindamycin, ciprofloxacin, PPI, renal replacement therapy | Partial thrombosis of the common femoral vein | alive |
| 6 | 26 | M | Viral pneumonia | 145 | 56 | 61 | 6 | 2.1 | 6 | Anti-viral treatment, PPI | B/L digital ischemia in feet | alive |
| 7 | 40 | F | Legionella Pneumonia | 99 | 37 | 61 | 10 | 0.7* | 6 | ciprofloxacin, | Left femoral vein thrombosis and B/L digital ischemia in feet | alive |
| 8 | 61 | M | Pneumococcal pneumonia | 214 | 61 | 70 | 8 | 3.1 | 5 | Multi-organ failure, renal replacement therapy, | Extensive thrombosis in abdominal vessels and | dead |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | ceftriaxone | splenic and liver infract | |

ECMO= extracorporeal membrane oxygenation; M= male; F=female; HIT= heparin induced thrombocytopenia; B/L= bilateral; * samples were tested with alternative immunoassay with Hemosil® AcuStar HIT-IgG (PF4-H) and results were positive for both patients

**Supplemental Table 2. Characteristics of patients diagnosed as heparin induced thrombocytopenia on veno-arterial extracorporeal membrane oxygenation**

| Patient | Age | sex | Indication for ECMO | Platelet count at the initiation of ECMO (109/L) | Platelet nadir (109/L) | % decrease in platelet count at the diagnosis of HIT | Duration in EMCO at the diagnosis of HIT | HIT ELISA OD value | PTPS | Cause of thrombocytopenia<br><br>Other than HIT and being on ECMO | Thrombotic event | 30-day outcome |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 22 | M | Cardiac arrest, pericardial effusion and IPAH | 216 | 45 | 74 | 6 | 2.5 | 4 | Multi-organ failure, teicoplanin, PPI, renal replacement therapy | Thrombosis in femoral artery, multiple thrombosis in IVC, right iliac and femoral veins, thrombosis in right atrial appendages | Dead |
| 2 | 51 | F | Cardiogenic shock of unknown | 158 | 56 | 63 | 5 | 1.5 | 5 | Multi-organ failure, PPI, renal replacement | Right femoral artery | Dead |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | aetiology Fulminant myocarditis | | | | | | | therapy | thrombosis | |
| 3 | 45 | M | Myocarditis | 165 | 61 | 60 | 7 | 2.0 | 4 | Multi-organ failure, renal replacement therapy | Ischemic right leg requiring amputation | Dead |
| 4 | 35 | M | Cardiogenic shock secondary to severe MR secondary to posterior mitral valve leaflet prolapse | 210 | 43 | 78 | 6 | 1.8 | 6 | Multi-organ failure, teicoplanin, PPI, renal replacement therapy | Partially occlusive thrombus in coeliac trunk causing ischemia of liver, kidney and pancreas, developed | Dead |
| 5 | 57 | F | Viral myocarditis | 145 | 38 | 73 | 9 | 2.1 | 4 | Linezolid, PPI | B/L PE | Alive |
| 6 | 60 | M | Cardiogenic shock, severe dilated cardiomyopathy | 138 | 41 | 70 | 6 | 2.9 | 5 | Anti-arrhymic drugs, diuretics | Ischemic toes | Alive |
| 7 | 30 | F | Toxic | 250 | 62 | 75 | 7 | 3.0 | 4 | Liver failure, PPI, | Right | Alive |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | cardiomyopathy secondary to possible drug overdose and aspiration pneumonia | | | | | | | Tazocin | femoral artery thrombosis | |
| 8 | 45 | M | Dilated cardiomyopathy | 116 | 40 | 65 | 10 | 0.9* | 7 | Anti-arrhymic drugs, diuretics | SVC thrombus | Alive |
| 9 | 47 | M | Acute lymphocytic myocarditis | 95 | 36 | 61 | 7 | 1.6 | 5 | Renal replacement therapy, Anti-arrhymic drugs, anti-viral treatment | cerebral infarction | Alive |
| 10 | 56 | M | Ischemic Cardiomyopathy | 170 | 51 | 67 | 8 | 2.3 | 5 | Beta blockers, diuretics | cerebral infarction, LIJ thrombus | Alive |
| 11 | 38 | F | Myocarditis | 121 | 19 | 79 | 11 | 3.5 | 3 | Diuretics, Beta blockers, renal replacement therapy | Left femoral artery thrombosis and ECMO cannula site thrombosis | Alive |

ECMO= extracorporeal membrane oxygenation; M= male; F=female; HIT= heparin induced thrombocytopenia; B/L= bilateral; IPAH= Idiopathic pulmonary arterial hypertension; MR= mitral regurgitation * Sample was tested with alternative immunoassay with Hemosil® AcuStar HIT-IgG (PF4-H) and result was positive