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Research Article

Exploring the Prevalence of Low Antithrombin III Level among Post-cardiac Surgery Patients and its Impact on Heparin Efficacy

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Abstract

Background: Antithrombin III (ATIII) is a plasma protein that prevents stimulated clotting factors from functioning. Heparin binds to ATIII and potentiates its anticoagulant action by inactivating thrombin pro-coagulant activity. Heparin resistance due to ATIII deficiency is common among post-cardiac surgery patients, but limited evidence concerning the prevalence of low ATIII levels in such patients exists. **Objective**: The main objective of this study was to investigate the prevalence of low ATIII levels among post-cardiac surgery patients and assess ATIII's correlation with the anticoagulant response of unfractionated heparin (UFH). **Methods**: This study was a retrospective cohort study for which all patients who underwent cardiac surgery from May 2008 to May 2018 at our center were screened. ATIII deficiency was defined as plasma ATIII levels <60%. **Results**: We screened 300 adult patients who underwent cardiac surgery during the study period, and 100 out of the 300 patients fulfilled the selection criteria. The prevalence rate of low ATIII was 42/100 (42%) with a mean level of 64.7% ± 27.6%. Among the 67 patients who received UFH, the correlation between lower ATIII levels and higher coagulation parameters on day 1 of heparin therapy was negative but not significant ($p \geq 0.05$). On day 2, there was significant negative correlation ($p < 0.05$), lower ATIII level indicated a tendency to achieve higher aPTT, aPTT ratio, and anti-Xa, with a modest magnitude of correlation (38%, 37%, and 47%, respectively). After 72 h, this correlation disappeared. Majority of the patients 41/67 (61.2%) achieved target aPTT ratio during the first 48 hrs. Heparin resistance was reported in 5/67 (7.5%). **Conclusion and Relevance**:

The prevalence of low ATIII levels in post-cardiac surgery patients was remarkably high. There is a negative correlation between ATIII levels and achieving the therapeutic anticoagulation target during the early days after surgery.

Keywords: Antithrombin III; Anticoagulation; Heparin; Activated Partial Thromboplastin Time

Abbreviation: ATIII: Antithrombin III; UFH: Unfractionated Heparin; IRB: Institutional Review Board; aPTT: The Activated Partial Thromboplastin Time

Introduction

The administration of an effective anticoagulant post-cardiac surgery is critical for reducing morbidity and mortality. During cardiac surgery, unfractionated heparin (UFH) is commonly used as the drug of choice for preventing and treating thrombosis [1,2]. Heparin attaches to antithrombin III (ATIII) and stimulates the action of ATIII, consequently catalyzing the inactivation of the pro-coagulation process. Antithrombin III is a biological plasma protein that prevents stimulated clotting factors from functioning. [3,4]

Antithrombin III concentration in the plasma can interfere with the effects of heparin and lead to heparin resistance [5]. Heparin resistance in adults is defined as a heparin infusion rate that reaches ≥ 35 units/kg /h with no laboratory evidence of response measured by the activated partial thromboplastin time (aPTT) ratio or anti-Xa assay [6]. To measure the effects of heparin, laboratory monitoring is recommended. aPTT and the anti-Xa are the most frequently used indicators for heparin efficacy. The activated clotting time (ACT) is also used to monitor treatments with high heparin doses. [2,3,6-9]

Multiple studies have been conducted to determine the association between ATIII level and heparin resistance. In three prospective studies, the possible association of ATIII and heparin resistance was explained [10–12]. The data in these studies established the high occurrence of heparin resistance in cardiac surgery patients [13,14]. Currently, not enough evidence on the prevalence of low ATIII levels in cardiac surgery settings exists. This study aimed to determine the prevalence of low ATIII levels among post-cardiac surgery patients. Additionally, we aimed to assess the correlation of plasma ATIII levels with the anticoagulant response of UFH.

Methods

Patients

This study was conducted as a retrospective, single-center cohort study that enrolled patients admitted to the adult cardiac surgery intensive care unit (CSICU) with documented ATIII levels from May 2008 to May 2018 at our tertiary care institution. Exclusion criteria included pediatric patients (≤ 18 years) and patients admitted to CSICU beyond the timeframe of this study. The study was approved by King Faisal Specialist Hospital and Research Centre's (KFSH&RC) Institutional Review Board (IRB). Data were collected from patients' electronic medical records using REDCap 8.9.0 software.

Our Heart Centre specializes in bypass surgery, invasive and noninvasive surgery, and interventional cardiology. It is the only center for heart transplantation in the Gulf region and is accredited by the Joint Commission International, the Society of Cardiovascular Patient Care, Cardiovascular Excellence, and European Laboratory Accreditation through the European Society of Cardiology and the European Association of Cardiovascular Imaging.

Primary and Secondary Endpoints

The primary endpoint was to determine the prevalence of ATIII deficiency in post-cardiac surgery patients. The 2021 ELSO guidelines recommend targeting an ATII of >50-80%. We used a cutoff of <60% as it would be more clinically relevant [6]. Additionally, according to the organization standard reference, ATIII deficiency is defined as an ATIII plasma level of less than 60%.

The secondary endpoints was to study whether any correlation existed between ATIII level and heparin efficacy in post-cardiac surgery patients. This objective was achieved by investigating the capability of patients to achieve target partial thromboplastin time (PTT)-ratio, aPTT, and anti-Xa assay at 24, 48, and 72 h, despite the protocol used; low or high-dose heparin, extracorporeal membrane oxygenation (ECMO), and use of ventricular assist devices (VADs) as shown in Appendix.

Additional secondary endpoints include heparin resistance, defined as a heparin infusion rate that reaches ≥ 35 units/kg /h with no laboratory evidence of response measured by aPTT ratio or anti-Xa assay [6].

Safety endpoints

Safety endpoints included the rate of bleeding and thrombocytopenia. Major bleeding was defined as the rate of blood loss of at least 2 g/dl in 24 h, greater than 20 ml/kg over a 24 h period, and/or a transfusion of 10 mL/kg packed red blood cells (PRBC) or more over that same period. Any bleeding that was retroperitoneal, pulmonary, or involved the central nervous system or bleeding that required surgical intervention was also considered major bleeding. Minor bleeding is defined as all reported bleeding not classified as major.10 Heparin-induced thrombocytopenia was defined as a 30% decrease in platelet count to < 100×10^9/l or a drop of > 50% from the patient's baseline platelet count [16].

Statistical Analysis

All categorical variables, such as gender and risk factors, are represented by numbers and percentages. Continuous variables as mean ± standard deviation (SD). Non-normally distributed data are presented as median and interquartile ranges. Regarding inferential statistics for correlation analysis, we used the log-rank test. A P-value < 0.05 is considered statistically significant. Data were analyzed using JMP Pro 13 software and are presented in tables and graphs.

Results

Out of the 300 patients screened during the study period, a total of 100 patients were included. Sixty-seven were on heparin of which 77.6% followed the low-dose heparin protocol (Figure 1). Fifty-six percent of the study population were male with an average age of 43.3 ± 15.4 years and an average weight of 71.1 ± 20.8 kg. In our study population, 38% of patients had heart failure, 28% had hypertension, and 27% had diabetes mellitus. Most patients had undergone previous surgeries, 13% underwent valve repair, and 12% had received a valve replacement. Most patients were on anticoagulant or antiplatelet therapy, 38% on heparin, and 21% on aspirin. Thirty percent of patients had previously used heparin in the past (Table 1). The type of cardiac surgical admission is summarized in Table 2. (Figure 1, Table 2).

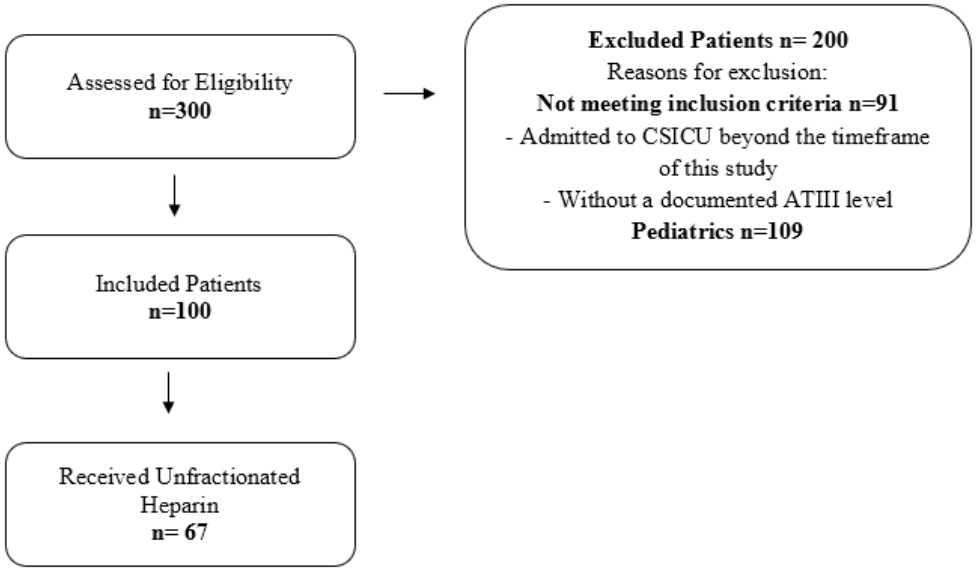


Figure 1: Patients Screening (N=300)

Characteristic		N = (100)
Age, yr (Mean ± SD)		43.3 ± 15.4
Gender	Male	56%
	Female	44%
Weight, kg		71.1 ± 20.8
Height, cm		163.1 ± 10.24

Surgical History, patients %	Valve replacement	13
	ICD	12
	ECMO	12
	Heart transplant	10
	PCI	5
	CABG	3
	VAD	3
	Pacemaker	3
	Valve replacement	2
Past Medical History, %	Heart Failure	38
	HTN	28
	DM	27
	Rheumatic Heart Disease	23
	Pulmonary HTN	22
	Atrial fibrillation	17
	Pulmonary embolism	11
	Dyslipidemia	9
	Chronic Kidney Disease	9
	ACS	7
	DVT	7
	Stroke	7
	Cancer	5
	Congenital Heart Disease	5
	Thyroid	4
	Chronic Stable Angina	3
	Liver disease	3
	Hematologic Disorders	2
	Anemia	2
	Arrhythmia	1
	COPD	1
Previous use of heparin, %	Yes	30
	Unknown	70
Patient medications before surgery, %	Heparin	38
	Aspirin	21
	Enoxaparin	13
	Warfarin	13
	Rivaroxaban	3
	Clopidogrel	2

Baseline Lab Values	Hemoglobin(g/dl)	115.06± 25.74
	Platelets (10*9/L)	244.2± 124.6
	ACT(sec)	182.9± 34.02
	aPTT (sec)	44.3± 17.9
	APTT(ratio)	1.36± 0.62
	ATIII (%)	64.7% ± 27.6%
Abbreviations: ACS; acute coronary syndrome, ACT; activated clotting time, aPTT; activated partial thromboplastin time, ATIII; Antithrombin III, CABG; coronary artery bypass graft, COPD; chronic obstructive pulmonary disease, DM; diabetes mellitus, DVT; deep vein thrombosis, ECMO; extracorporeal membrane oxygenation, HTN; hypertension, ICD; implantable cardioverter-defibrillator, PCI; percutaneous coronary intervention, VAD; ventricular assist devices.		

Table 1: Baseline Characteristics (N=100)

Type of surgery	Patients (%)
Valve replacement:	35
Mechanical	9
Biosynthetic	7
CABG	10
VAD	40
Heart transplant	19
ECMO	13
Central line catheter	3
CPB time, min	114.5 ± 52.7
Abbreviations: CABG; coronary artery bypass graft, CPB; Cardiopulmonary bypass, ECMO; extracorporeal membrane oxygenation, VAD; ventricular assist device	

Table 2: Types of Cardiac Surgery Performed (N=100).

Primary endpoint

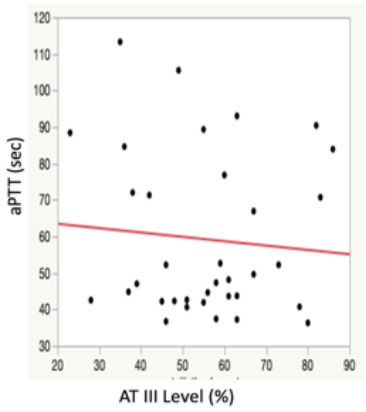
Of the 100 study patients, 42% had low ATIII levels, while 58% had normal ATIII concentrations ranging from 60% to 120% with a mean value of 64.7% ± 27.6%.

Secondary endpoint

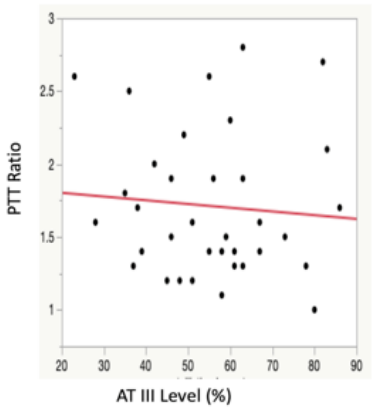
Most patients achieved the aPTT ratio target on day one of heparin therapy 28/67 (41.7%, (Figure 2)). The correlation between ATIII levels and PTT-ratio, aPTT, and anti-Xa for 67 patients who were on post-cardiac surgery heparin was assessed. The correlation between ATIII level and PTT-ratio, aPTT, and anti-Xa on day one of heparin therapy trended downward; however, it was not significant with p-values of 0.6405, 0.6268, and 0.6515, respectively (Figure 2a).

On day two, however, the correlation was shown to be significant with a clear negative correlation and p-values of 0.0292, 0.0249, and 0.0421, respectively (Figure 2b). A lower ATIII level indicated a tendency to achieve higher aPTT, aPTT ratio, and anti-Xa, with a modest magnitude of correlation (38%, 37%, and 47%, respectively). On day three, interestingly, this correlation disappeared (Figure 2c).

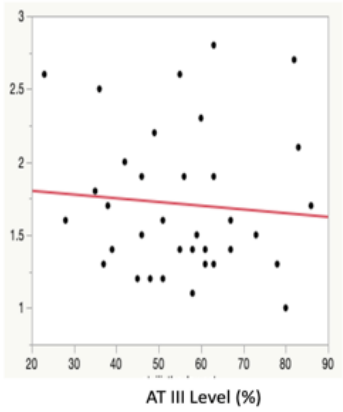
Panel (a)



p-value = 0.626
r =0.085



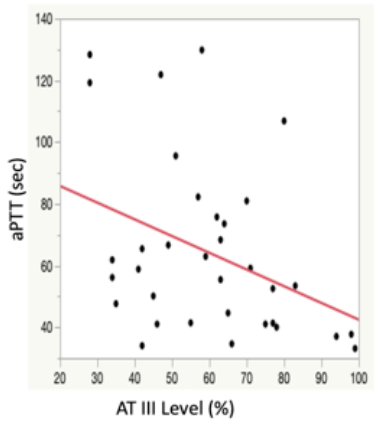
p-value = 0.640
r = 0.082



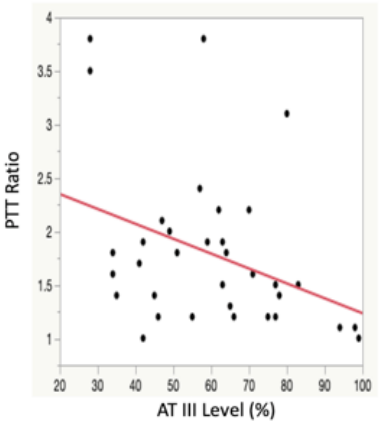
p-value = 0.65
r = 0.127

Panel (b)

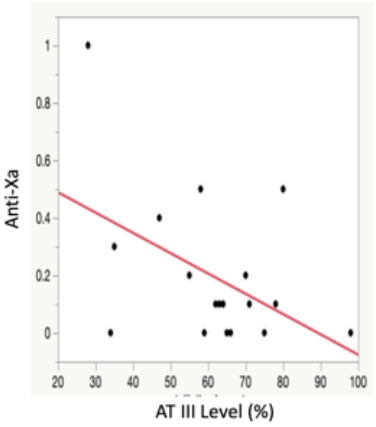
p-value = 0.025
r = 0.38



p-value = 0.0292
r = 0.37



p-value = 0.042
r = 0.47



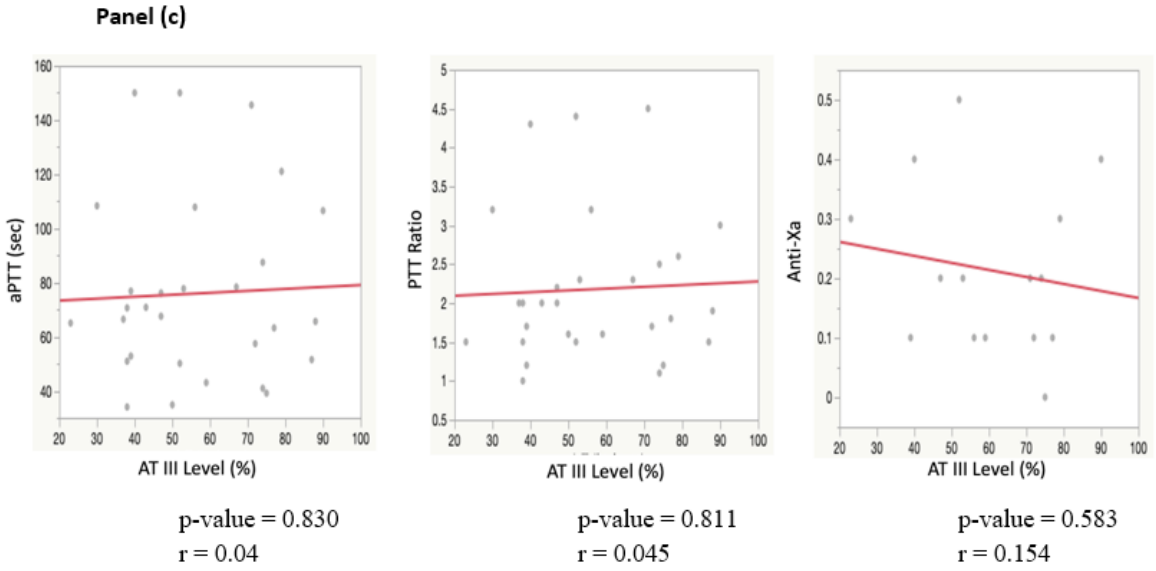


Figure 2: The Correlations between ATIII level and aPTT, PTT-ratio, and anti-Xa on Day 1 (panel a), Day 2 (panel b), and Day 3 (panel c)

The probability of achieving the target aPTT ratio in relation to time in hours in patients with normal ATIII versus patients with low ATIII was tested using a log-rank test as shown in Figure 3. Patients with lower ATIII levels had numerically higher chances of achieving their target aPTT ratio earlier than patients with normal levels; however, the difference between the two groups was not statistically significant (p = 0.86). A univariable Cox regression analysis showed that no evidence of a relationship between the ATIII level (on a continuous scale) and the time to reaching the target level existed; p-value = 0.60 and 95% confidence interval (CI) of 0.98–1 (Figure 3). Utilizing our study definition, 6 out of the 67 patients who were on heparin, five patients (7.5%) developed heparin resistance

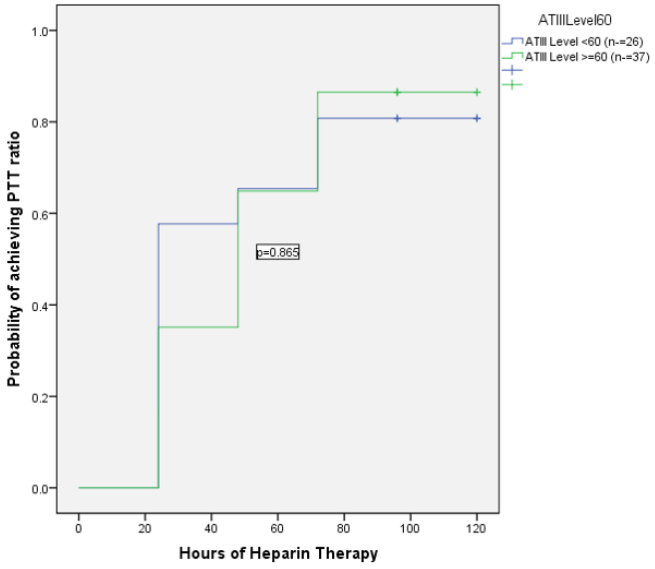


Figure 3: The probability of achieving target aPTT ratio in relation to time in hours and Antithrombin III (ATIII) level (N=63)

Safety endpoints

The rate of overall bleeding was 54%, and 50% of those were classified as major bleeding events. Suspected heparin-induced thrombocytopenia (HIT) was reported in 34 out of 100 patients.

Discussion

Reaching the target PTT ratio is considered a predictor of heparin response among patients receiving UFH. In our organization, we utilize two different heparin protocols, namely, high and low-dose anticoagulation. The selection of one protocol over the other is based on the indication and the dose of anticoagulation needed. However, in our post-cardiac surgery patients, the presence of bleeding is an essential determinant. The target aPTT ratio of low dose heparin (starts with a rate of 15 units/kg/h) is a range of 1.5–1.9, whereas the target aPTT ratio representing the high dose (starts with a rate of 18 units/kg/h) is between 2 and 2.5. Pharmacologically, UFH activity relies on ATIII, which might become depleted during surgery due to bleeding and the use of cardiopulmonary bypass [17]. However, we do not know the actual prevalence of ATIII in this cohort of patients and its relation to achieving the target aPTT ratio or heparin resistance in a post-cardiac surgery settings. Our study sought to answer these fundamental questions.

The mean ATIII level in our cardiac surgery patients was 64.7% ± 27.6%, which is within the ATIII normal range of >60%, however the prevalence of low ATIII was 42%. Many contributing factors, including the complexity of the surgery in our referral cardiac surgery center, may explain the high prevalence. Almost 30% of our patients had undergone prior valve surgery, 20% had undergone a heart transplant, and 13% were on ECMO, and it is known that they present a higher risk for surgery. Despite these conditions, we believe the prevalence is remarkably high. Interestingly, the prevalence of heparin resistance in our population was 7.5%, which is lower than the reported incidence among CABG patients [12]. Three cohort studies were conducted to investigate the ATIII level in relation to cardiac surgery and its impact on heparin activity. Available data confirmed the high incidence of heparin resistance and identified a positive relationship between baseline ATIII level and heparin resistance [11, 12, 15]. The results of one of a single large study that included 500 patients undergoing coronary artery bypass graft (CABG) surgery reported that 104 patients (20.8%) had heparin resistance, as compared to 7.5% in our study [11].

Using a holistic outlook of the scatterplots over the first three days post-surgery, it can be seen that a trend toward a negative correlation between ATIII level and UFH activity represented by aPTT, aPTT-ratio, and anti-Xa on day one was noted, was obviously significant by day two, and disappeared by day three. Lower ATIII levels corresponded with higher anticoagulation indices; thus, it appears under these conditions that more patients will achieve the target aPTT-ratio and/or anti-Xa target. Indeed, 47% of the patients achieved target aPTT ratio during the first 24 hours and 61% during the first 48 hrs. If we use the same dosing of UFH in the presence of low ATIII levels, it is logical that heparin will be more likely to bind to more ATIII and potentiate its effect. This supposition was clearly demonstrated within 48 h of therapy. This result was unexpected since other studies have suggested rather contrary results [11-15] Yet, the replacement of ATIII with antithrombin III products (Thrombate III® and Atenativ®) or fresh frozen plasma (FFP) is not the standard of practice. Clinically, it would require a high volume of FFP to replenish ATIII in our patients, who are already fluid-overloaded and fluid-restricted. Additionally, the currently available products have both availability and cost limitations. Furthermore, the use of ATIII as a replacement might be associated with deleterious effects such as bleeding, hematoma, and chest pain.

Another confounder that might have influenced the correlation was the use of FFP. About 40% of our patients received FFP transfusions during surgery. Four patients in the heparin resistance group received FFP (80%), and 3/5 (60%) had low ATIII levels, with no significant correlation.

This procedure may have caused an increase in the level of ATIII in the plasma thus altering the patient's response to heparin. However, we measured ATIII level in the CSICU after surgery regardless of the use of FFP. It is worth mentioning that the use of FFP is very common in cardiac surgery. Overall, the trend was toward a correlation for the first day after surgery, which then became significant, although modest, in magnitude the day after (day 2). This finding has a major clinical implication regarding the decision on replacing ATIII in patients who fail to achieve aPTT target in this particular clinical setting.

The frequency of adverse effects, such as bleeding and suspected HIT, was also high in our study. Half of our patients developed some form of bleeding, and out of those, 50% had major bleeding events. HIT is a destructive immune-initiated adverse drug reaction that occurs due to the formation of antibodies that activate platelets and potentially lead to dangerous complications, such as thrombosis. Thirty-seven percent of our patients who received heparin in the study had suspected HIT. However, the confirmed prevalence of HIT in a different cohort at our institution was reported to be 0.68% [18].

Limitations

This study presented some drawbacks, such as its retrospective, single-center nature, which made it difficult to gather all study-related data and limited our sample size. In addition,

our study included patients who had undergone complex cardiac surgeries, including heart transplants and ECMO placement.

Conclusions and Relevance

The prevalence of low ATIII level among cardiac surgery patients is remarkably high. Unlike previous studies, our study showed a negative, yet modest, correlation between ATIII level and achievement of therapeutic anticoagulation targets, particularly on the second day of therapy. Furthermore, new prospective studies are warranted to explore this relationship among patients who undergo complex cardiac surgery.

Declarations

Ethical Approval: The study was conducted following KFSH&RC policies and procedures included in those for the Research Advisory Council (RAC). For concerns of patient confidentiality and safety, the data was retrieved from the hospital integrated clinical information system (ICIS). All patients were anonymized and a log sheet was used to link the created serial numbers with patients and the document stays with the primary investigator to assure patient privacy. Only the study investigators have access to the data. Due to the nature of this study, there is no need for an informed consent form as it carries no additional risk for these patients apart from the standard of practice.

Funding: Not applicable

Availability of data and materials: The data was retrieved from the hospital's integrated clinical information system (ICIS). All patients were anonymized and a log sheet was used to link the created serial numbers with patients and the document stays with the primary investigator to assure patient privacy. Only the study investigators have access to the data.

Disclosures: The Authors of this study have nothing to disclose concerning financial or personal relationships with commercial entities that may have a direct or indirect interest in the subject matter of this presentation.

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