Review Article

Incidence of Heparin Resistance during Cardio-Pulmonary Bypass in Adult Cardiac Surgery in the Era of COVID-19

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ABSTRACT

Introduction: Amazing breakthroughs in cardiac surgery have been made possible by the use of cardiopulmonary bypass (CPB), which has made the operating field motionless and bloodless. It wasn't until the introduction of heparin and its powerful antidote, protamine, that it was possible to safely establish anticoagulation in the within the extracorporeal circuit (ECC) and then reverse it after surgery. However, some people may develop heparin resistance during CPB, resulting in subtherapeutic ACT levels because they are less sensitive to heparin. The thromboembolic phenomenon, severe postoperative bleeding, and consumptive coagulopathy are only a few risks that might arise from insufficient anticoagulation.

Objective: To calculate the prevalence of heparin resistance in adult cardiac surgery undergoing cardio-pulmonary bypass in the COVID-19 period.

Patients and Methods: For that we enrolled 229 selected from the patients would undergo Cardiac surgery using cardio-pulmonary bypass, all cases confirmed to have covid-19.

Results: In the current study, we estimated heparin resistance after preoperative heparin therapy. ACT-based definition of heparin resistance was used in our study (ACT less than 400 seconds after 300 U/kg heparin), we found the mean baseline ACT was 112.7 ± 9.2, the mean heparin loading was 5.9 ± 0.8 amp and, the mean post-loading ACT of all studied patients was 536.6 ± 108.1 and of all studied 229 patients, there were 21 patients (9.2%) with heparin resistance. In the present study, the extra heparin was used among 21 cases the mean extra heparin used was 2.9 ± 0.3 amp with minimum extra heparin of 2 amp and maximum extra heparin of 3 amp. And the mean post-extra ACT was 406.8 ± 116.02 with minimum post-extra ACT of 280 and maximum post-extra ACT of 615. Furthermore, there were 15 patients (71.4%) of heparin resistance needed FFP. The mean needed FFP was 1.93 ± 0.25 units, and the mean post-FFP ACT was 638.2 ± 95.5 with minimum post-FFP ACT of 521 and maximum post-FFP ACT of 845.

Conclusion: According to the findings, 9.2% of adult cardiac surgery patients experience heparin resistance during cardio-pulmonary bypass in the COVID-19 era.

Key Words: Adult cardiac surgery; cardio-pulmonary bypass; COVID-19; heparin resistance.

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INTRODUCTION

Because CPB allows for a bloodless and immobile operative area, it has revolutionized and greatly advanced the field of cardiac surgery. Heparin was used to solve the technical difficulty of avoiding thrombosis within the ECC, enabling safe anticoagulation to be instituted and then reversed at the conclusion of operation[1].

A naturally occurring mucopolysaccharide, heparin, to variable degrees facilitates the coagulation of antithrombin III (AT III) and other coagulation proteases. Heparin therapy is used in many different therapeutic contexts. Achieving the treatment target within a short time frame is crucial to maximize benefit, considering the severity of the illnesses treated with heparin. Additionally, anticoagulation is necessary for processes like CPB and hemodialysate[2].

Subtherapeutic ACT levels can result from heparin resistance, or a patient's diminished response to heparin, which can happen in certain individuals undergoing CPB. Insufficient anticoagulation may cause the coagulation cascade to be activated, which might result in problems such as thromboembolic phenomena, excessive postoperative bleeding, and consumptive coagulopathy. Due to the

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undetermined target ACT, which strikes a compromise between the dangers of excessive bleeding and circuit thrombosis, a range of ACT targets, from 400 to 500 seconds, are employed in clinical practice for the start and maintenance of CPB. Because of this, several criteria have been applied in the literature to define heparin resistance, with differing emphasis on the first bolus dosage of heparin and the goal ACT for starting CPB[3,4].

When standard-of-care heparin fails to reach the goal ACT, there are now four major therapies to establish enough anticoagulation in cardiac operations such as extracorporeal membrane oxygenation (ECMO) or CPB[5]. These consist of administering more heparin, supplementing with FFP or an AT concentrate (purified or recombinant), administering a different anticoagulant, or not administering any extra medication[6].

Anecdotal case reports and finally observational studies have shown a greater prevalence of thromboembolic events in critically sick patients infected with COVID-19 despite anticoagulation since SARS-CoV-2 first appeared in Wuhan city, Hubei province, China, in December 2019. These patients are more susceptible to thrombosis due to the underlying hypercoagulopathy and hyperinflammatory processes triggered by the COVID-19 infection. Additionally, these processes may also play a role in the development of heparin resistance in the critical care unit and during CPB[7].

AIM OF THE WORK

The aim of this study is to estimate the incidence of heparin resistance during cardio-pulmonary bypass in adult Cardiac surgery in the era of covid-19.

TYPE OF STUDY

Cross sectional study.

PLACE OF STUDY

Souad kafafi University hospital, welcare hospital.

STUDY PERIOD

18 months from jan/2023 to july/2024.

PATIENTS AND METHODS

This cross sectional study included 229 participants who were selected from the patients who underwent cardiac surgery using cardio-pulmonary bypass within a period of 18 months.

Participants in the research comprised adult patients > 18 years old of both sexes, as well as those having a history of proven Covid-19 infection and immunization history. However, participants with known coagulation abnormalities, severe liver illness, renal failure, or cancer were not allowed to participate in the trial.

An analytical cross-sectional research with the primary goal of estimating the incidence of heparin resistance after adult cardiac surgery's cardio-pulmonary bypass in the COVID-19 period. According to a prior study, 8.06% of patients developed heparin resistance following preoperative heparin therapy[8]. Thus, 129 patients at minimum were enrolled in the research.

Ethical consideration

Approval from Faculty of Medicine Ain Shams University ethical committee was obtained (No. FWA000017585; Date: 25/10/2023). Informed consent would be taken from every participant after explaining the purpose of the study.

All research participants received an explanation of the following basic guidelines: participation in this study is entirely voluntary and free of charge. He may not directly profit from his participation in this study, but other patients may gain from the data collected. The patient may opt out of this research at any time, for any reason, at any time. The study's findings may be published in a scholarly journal, but the patients' identities remained completely private.

All patients were subjected to an informed consent, Demographic data, Complete history taking, complete physical examination, operation type, laboratory examination (with special emphasis on CBC, renal function, liver function and coagulation profile and detailed covid19 infection data and detailed vaccination data.

Patients presenting in the preoperative critical care unit of the operating room for heart surgery with cardiopulmonary bypass were examined.

After receiving heparin medication prior to surgery, the patients were assessed for heparin resistance. Heparin resistance is defined by the ACT-based approach (ACT less than 400 seconds after 300 U/kg heparin)[8].

Cardiopulmonary bypass was initiated upon the confirmation of sufficient ACT in normothermia or mild hypothermia (34°C) with topical cooling. To reach the desired ACT value, 400 seconds of heparinization with 300 IU kg-1 unfractionated heparin was used. A Hemochron 401 coagulation monitoring equipment (Technidyne Corp., Edison, NJ, USA) was utilized to measure ACT. After CPB was withdrawn, protamine sulphate was administered in a 1:1 ratio to reverse the original heparin dosage. A questionnaire was created to assess heparin resistance following preoperative heparin medication. The questionnaire includes possible predicted parameters such as demographics, pre, intraoperative, and post-operative variables.

Statistical analyses

Data were gathered, edited, categorized, and put into SPSS version 20. Qualitative data were presented as numbers and percentages, and quantitative data were given as means, standard deviations, and ranges. The confidence interval was set at 95%, and the acceptable margin of error was 5%.

RESULTS

Table 1 provides the demographic characteristics for all of the patients investigated. The average age of all analyzed patients was 55.1 ± 9.6 years, with a range of 28 to 78 years. The study included 148 males (64.6%) and 81 females (35.4%). The average weight of all analyzed patients was 79.05 ± 17.2, with a minimum of 48 and a high of 117.

Table 1: Description of demographic data in all examined patients

		Studied patients (N = 229)	
Sex	Male	148	64.6%
	Female	81	35.4%
Age (years)	Mean ±SD	55.1 ± 9.6	
	Min - Max	28 – 78	
Weight (kg)	Mean ±SD	79.05 ± 17.2	
	Min - Max	48 – 117	

The chronic illness descriptions for every subject in the study are displayed in (Table 2). 162 patients (70.7%) had DM, while 135 patients (59%), had HTN. 100% of the patients in the study tested positive for COVID-19.

Table 2: Description of chronic diseases in all examined patients.

		Studied patients (N = 229)	
DM	No	67	29.3%
	Yes	162	70.7%
HTN	No	594	41%
	Yes	135	59%
COVID-19	No	0	0%
	Yes	228	100%

(Table 3) shows the description of operation in all examined patients.

Table 3: Description of operation in all examined patients.

		Studied patients (N = 229)	
Operation	AVR	12	5.2%
	AVR + MVR + ASD	1	0.4%
	BENTALL	6	2.6%
	CABG	112	48.9%
	CABG + MVR	14	6.1%
	CABG + MVR + TVR	1	0.4%
	DVR	27	11.8%
	DVR + TVR	1	0.4%
	MVR	42	18.3%
	MVR + TVR	11	4.8%
	TVR	2	0.9%

(Table 4) shows the description of baseline ACT, loading heparin & post-loading ACT in all studied patients. As regards baseline ACT, the mean baseline ACT of all studied patients was 112.7 ± 9.2 with minimum baseline ACT of 84 and maximum baseline ACT of 145. As regard heparin loading, the mean heparin loading of all studied patients was 5.9 ± 0.8 amp with minimum heparin loading of 4 amp and maximum heparin loading of 8 amp. As regards post-loading ACT, the mean post-loading ACT of all studied patients was 536.6 ± 108.1 with minimum post-loading ACT of 175 and maximum post-loading ACT of 785.

Table 4: Description of baseline ACT, loading heparin & post-loading ACT in all studied patients.

		Studied patients (N = 229)
ACT (baseline)	Mean ±SD	112.7 ± 9.2
	Min - Max	84 – 145
Heparin loading (amp)	Mean ±SD	5.9 ± 0.8
	Min - Max	4 – 8
ACT (post-loading)	Mean ±SD	536.6 ± 108.1
	Min - Max	175 – 785

(Table 5) shows the description of heparin resistance in all studied patients. Of all studied 229 patients, there were 21 patients (9.2%) with heparin resistance.

Table 5: Description of heparin resistance in all studied patients

		Studied patients (N = 229)	
Heparin resistance	No	208	90.8%
	Yes	21	9.2%

(Table 6) shows the description of extra-heparin & post-extra ACT in heparin resistant patients. As regards extra heparin, the mean extra heparin was 2.9 ± 0.3 amp with minimum extra heparin of 2 amp and maximum extra heparin of 3 amp. As regards post-extra ACT, the mean post-extra ACT was 406.8 ± 116.02 with minimum post-extra ACT of 280 and maximum post-extra ACT of 615.

Table 6: Description of extra-heparin and post-extra ACT in patients with heparin resistance.

		Heparin resistant patients (N = 21)
Extra heparin (amp)	Mean ±SD	2.9 ± 0.3
	Min - Max	2 – 3
ACT (post-extra)	Mean ±SD	406.8 ± 116.02
	Min - Max	280 – 615

(Table 7) shows the description of FFP and post-FFP ACT in heparin resistant patients. There were 15 patients (71.4%) of heparin resistance deeded FFP. The mean needed FFP was 1.93 ± 0.25 units with minimum FFP of 1 unit and maximum FFP of 2 units. As regards post-FFP ACT, the mean post-FFP ACT was 638.2 ± 95.5 with minimum post-FFP ACT of 521 and maximum post-FFP ACT of 845.

Table 7: Description of FFP and post-FFP ACT in patients with heparin resistance.

		Heparin resistant patients (N = 21)	
FFP need	No	6	28.6%
	Yes	15	71.4%
FFP (units)	Mean ±SD	1.93 ± 0.25	
	Min - Max	1 – 2	
ACT (post-FFP) (N = 15)	Mean ±SD	638.2 ± 95.5	
	Min - Max	521 – 845	

(Table 8) shows the description of ACT on bypass and at 1st hour in all studied patients. As regards ACT on bypass, the mean ACT was 661.1 ± 65.9 with minimum ACT of 504 and maximum ACT of 1060. As regards ACT at 1st hour, the mean ACT was 937.7 ± 50.5 with minimum ACT of 869 and maximum ACT of 990. At 2nd hour there was only 1 patient with an ACT of 1074.

Table 8: Description of ACT on bypass and at 1st hour in all studied patients.

		Studied patients (N = 229)
ACT (on bypass)	Mean ±SD	661.1 ± 65.9
	Min - Max	504 – 1060
ACT (on 1st hour) (N = 4)	Mean ±SD	937.7 ± 50.5
	Min - Max	869 – 990

DISCUSSION

In the current study, we attempted to determine the incidence of heparin resistance during cardiopulmonary bypass in adult cardiac surgery in the age of COVID-19.

For this, we enlisted 229 patients who underwent heart surgery with cardiopulmonary bypass, all of whom were verified to have covid 19.

In the current investigation, the mean age of all analyzed patients was 55.1 ± 9.6 years, with male preponderance at 64.6%. Diabetes was observed in 70.7% and hypertension in 59%.

Similarly, Elderly patients (60.7±12.8 years), male(63.7%), hypertensive(75%), with CAD, with previous myocardial infarction, smokers, and diabetic (40%)were highly prevalent in Gomes *et al*.[9] series who investigated the clinical course and outcomes of patients submitted to cardiovascular surgery in Brazil and who had developed symptoms/signs of coronavirus disease 2019 (COVID-19) in the perioperative period. The same risk variables were shown to be associated with a poorer outcome in COVID-19[10-12].

According to recent research, those infected with SARS-CoV2 had higher levels of brain natriuretic peptide, CK, and occasionally troponin I. These findings indicate a myocardial damage at the disease's severe stages. It is widely documented that a dispersed inflammatory response can result in non-ischemic cardiac damage, including myocarditis. Myocardial damage was also diagnosed using electrocardiographic and echocardiographic abnormalities. Up to 17% of all hospitalized COVID-19 patients have this phenomenon, and up to 59% of cases of death experience it[13].

A decreased left ventricular ejection fraction in SARS-CoV2 infection is one of the signs of a general deterioration in ventricular function that recent research has connected myocarditis to. Ruan *et al*.[14] found that myocardial damage with circulatory failure and cardiac failure alone accounted for 33% and 7% of deaths, respectively, in a cohort of 150 patients.

Moreover, fulminant myocarditis was reported by Liu *et al*.[15]. Surprisingly, pathological examinations of this case report did not turn up any obvious histological abnormalities, such as inclusions of nuclear or cytoplasmic viruses in the cardiac fibers. This study suggests that SARS-CoV2 replication in cardiac tissue may not always be directly associated with heart damage.

We calculated heparin resistance following preoperative heparin medication in the current investigation. We used an ACT-based definition of heparin resistance in our study, which defined it as ACT less than 400 seconds after 300 U/kg heparin. Of the 229 patients we studied, 21 patients (9.2%) had heparin resistance. The mean baseline ACT was 112.7 ± 9.2, the mean heparin loading was 5.9 ± 0.8 amp, and the mean post-loading ACT was 536.6 ± 108.1.

The incidence of heparin resistance following preoperative heparin medication in patients having open heart surgery was found to be 8.06%, which is greater than the findings of a research by ***Naeem et al***.[8] that evaluated the same.

Additionally, 4.3% of the patients in Nissborg and Wahlgren's[16] study on the relationship between HR and postoperative complications in open heart surgery had an ACT of less than 400 seconds following the administration of 400 IU/kg heparin (the previous two studies did not assess covid 19 patients).

Furthermore, other research examined the heparin resistance in Covid-19, such as the observational cohort study by ***Nagler et al***.[17], which comprised individuals receiving extracorporeal carbon dioxide removal, venovenous ECMO, and venovenous ECMO. In the 197 patients included, 33 (16.8%) required UFH > 35 000 IU/d and 14 (7.1%) required UFH > 20 IU/kg/h. The primary risk factor was heparin resistance (UFH, > 35 000 IU/d or > 20 IU/kg/h).

A research conducted by ***Sattler et al***.[18] on patients who had severe acute respiratory distress syndrome associated to COVID-19 and needed to be on ECMO revealed retrospective data that indicated a considerably greater incidence of abnormalities in heparin response, surpassing 80% at a threshold of > 35 000 IU/d.

Eight out of ten patients developed resistance to therapeutic UFH, while five out of seven patients receiving therapeutic LMWH had unsatisfactory peak anti-Xa peaks, according to a prior research by ***White et al***.[19].

Similarly, all of the COVID-19 patients in ***Streng et al.***[20] observational research who were receiving continuous renal replacement therapy and ECMO met the criteria for heparin resistance.

Nonetheless, UFH > 35 000 IU/d was required in roughly 50% of (non-COVID-19) ECMO patients, according to an observational study by ***Raghunathan et al.***[21], while weight-based definitions with a cutoff of > 35 IU/kg/h in a prospective study by ***Panigada et al.***[22] carried out prior to the COVID-19 pandemic reported a 0% prevalence of heparin resistance.

Critically sick patients are often reported to have changed heparin response, but it is challenging to determine the true incidence of altered response since there are no standard criteria and insufficient observational data[23,24].

Because COVID-19 is a prothrombotic condition, patients not only had a considerably greater prevalence of changes in their heparin response, but they also had clotting events more often[25,26].

Some potential explanations for the high thromboprophylaxis failure rate observed in COVID-19 when conventional thromboprophylactic dosages are administered have been provided by ***Novelli et al.***[24] and ***White et al.***[19]. Acquired AT deficit in COVID-19 is uncommon, however it can happen to certain patients—even those who are not very sick. According to ***Novelli et al.***[24], there were no AT supplements given to any of the patients, and their mean AT levels were 83±17% (80%–120%).

Patients with COVID-19 often have high amounts of heparin-binding proteins linked to acute-phase responses[27]. Some pseudo-resistance may be anticipated in COVID-19 patients due to their high levels of FVIII and FIB, which artificially reduce the APTT level[28].

Heparin added to blood from COVID-19 patients produced lower-than-expected anti-Xa activity, according to in *vitro* experiments. This confirms that acute-phase proteins are the cause of the low heparin content. Resistance is once again confirmed by increased UFH clearance linked to an inflammatory state[19].

An observational study by ***Streng et al***.[20] of COVID-19 patients on ECMO and continuous renal replacement treatment found no link between heparin resistance and AT, factor VIII, fibrinogen, thrombocytes, C-reactive protein, or ferritin.

When patients show signs of an AT-dependent heparin resistance mechanism, the Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists advocate using AT concentrates during heart surgery. As an alternative, recommendations recommend using FFP during heart surgery if reduced AT levels are seen in conjunction with low coagulation factor levels, bleeding issues, or low fibrinogen levels[29].

Supplementation is routinely employed in clinical practice, as seen by the 82% of evaluated sites that used heparin in conjunction with AT concentrates, FFP, or pooled supplementation during ECMO operations[5,30]. In contrast to the usual dosages (300–400 U/kg plus extra doses) to reach or maintain the ACT, another investigation and review revealed that physicians treated cardiac patients with additional heparin doses as high as 1200 U/kg[6,30].

ACT levels after surgery may not reach goal levels even with large doses of heparin[6].

Patients who have developed heparin resistance see a normalization of their heparin/ACT dosage response curve when they get fresh frozen plasma. Additionally, the overall amount of heparin required decreases throughout CPB. These results imply the deficiency of one or more plasma-clotting factors[31].

In the present study, the extra heparin was used among 21 cases the mean extra heparin used was 2.9 ± 0.3 amp with minimum extra heparin of 2 amp and maximum extra heparin of 3 amp. And the mean post-extra ACT was 406.8 ± 116.02 with minimum post-extra ACT of 280 and maximum post-extra ACT of 615. Furthermore, there were 15 patients (71.4%) of heparin resistance needing FFP. The mean needed FFP was 1.93 ± 0.25 units, and the mean post-FFP ACT was 638.2 ± 95.5 with minimum post-FFP ACT of 521 and maximum post-FFP ACT of 845.

Alsagaff and Mulia[32] state that critical COVID-19 patients may get high-dose UFH for hemodialysis or ECMO, where ACT may be a monitoring option.

According to ***Rhoades et al***.[33], anti-Xa has been correlated to a decrease in UFH dosages, fewer UFH titrations, and a higher probability of reaching therapeutic levels.

When paired with a diminished response to UFH, the observed elevated incidence of thromboembolic consequences raised the possibility that changes in response to anticoagulation and heparin failure are causally related. Direct thrombin inhibitors were used more frequently in ECMO or CPB facilities as an anticoagulant tactic during COVID-19 as a result of this discovery[34].

CONCLUSION

According to the findings, 9.2% of adult cardiac surgery patients experience heparin resistance during cardio-pulmonary bypass in the COVID-19 period.

CONFLICT OF INTERESTS

There are no conflicts of interest.

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حدوث مقاومة للهيبارين أثناء المجازة القلبية الرئوية في جراحة القلب للبالغين في عصر كوفيد-١٩

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الخلفية: لقد أتاحت عملية المجازة القلبية الرئوية (CPB) في جراحة القلب الى إجراء عمليات جراحية غير دموية وغير متحركة، مما أدى إلى تطورات مذهلة. لم يكن الأمر كذلك حتى إدخال الهيبارين وترياقه القوي، البروتامين، حيث كان من الممكن إنشاء منع تخثر الدم بأمان في الدائرة خارج الجسم (ECC) ثم عكسه بعد الجراحة. ومع ذلك، قد يصاب بعض الأشخاص بمقاومة الهيبارين أثناء CPB، مما يؤدي إلى مستويات ACT تحت العلاج لأنهم أقل حساسية للهيبارين. إن اعتلال التخثر الاستهلاكي، والنزيف المفرط بعد العملية الجراحية، وظاهرة الانصمام الخثاري ليست سوى عدد قليل من المخاطر التي يمكن أن تنجم عن عدم كفاية منع تخثر الدم.

الهدف: تقدير حدوث مقاومة الهيبارين أثناء المجازة القلبية الرئوية في جراحة القلب للبالغين في عصر كوفيد-١٩.

الطرق: من أجل ذلك قمنا بتسجيل ٢٢٩ حالة تم اختيارها من المرضى الذين سيخضعون لجراحة القلب باستخدام المجازة القلبية الرئوية، وجميع الحالات مؤكدة إصابتها بكوفيد ١٩

النتائج: في الدراسة الحالية، قمنا بتقدير مقاومة الهيبارين بعد العلاج بالهيبارين قبل الجراحة. تم استخدام التعريف القائم على ACT لمقاومة الهيبارين في دراستنا (ACT أقل من ٤٠٠ ثانية بعد ٣٠٠ وحدة / كجم من الهيبارين)، ووجدنا أن متوسط خط الأساس ACT كان ١١٢,٧ ± ٩,٢، وكان متوسط تحميل الهيبارين ٥,٩ ± ٠,٨ أمبير، والمتوسط كان ACT بعد التحميل لجميع المرضى الذين شملتهم الدراسة ٥٣٦,٦ ± ١٠٨,١ ومن بين جميع المرضى الذين شملتهم الدراسة ٢٢٩ مريضًا، كان هناك ٢١ مريضًا (٩,٢٪) يعانون من مقاومة الهيبارين. في الدراسة الحالية، تم استخدام الهيبارين الإضافي بين ٢١ حالة، وكان متوسط الهيبارين الإضافي المستخدم ٢,٩ ± ٠,٣ أمبير مع الحد الأدنى من الهيبارين الإضافي ٢ أمبير والحد الأقصى للهيبارين الإضافي ٣ أمبير. وكان متوسط ACT بعد الإضافي ٤٠٦,٨ ± ١١٦,٠٢ مع الحد الأدنى بعد ACT الإضافي ٢٨٠ والحد الأقصى ACT بعد الإضافي ٦١٥. علاوة على ذلك، كان هناك ١٥ مريضًا (٧١,٤٪) من مقاومة الهيبارين بحاجة إلى FFP. كان متوسط FFP المطلوب ١,٩٣ ± ٠,٢٥ وحدة، وكان متوسط ACT بعد FFP ٦٣٨,٢ ± ٩٥,٥ مع الحد الأدنى من ACT بعد FFP البالغ ٥٢١ والحد الأقصى ACT بعد FFP البالغ ٨٤٥.

الاستنتاج: تشير النتائج إلى أن نسبة حدوث مقاومة الهيبارين أثناء عملية المجازة القلبية الرئوية في جراحة القلب للبالغين في عصر كوفيد-١٩ هي ٩,٢٪.