Oncology and Radiotherapy ©
Vol.17 Iss.12: 001-007 • RESEARCH ARTICLE

Perioperative coagulopathy in patients undergoing cytoreductive surgery and hyperthermic intraperitoneal chemotherapy

Joona Prabhakaran[1], Roopesh Sureshan[1], Jashma[1], Ratheesan Kumbakara[2]

[1] Department of onco-anaesthesiology, Malabar cancer centre, P.O. Moozhikkara, Kodiyeri, Thalassery, Kannur, Kerala, India

[2] Department of cancer registry, Malabar cancer centre, P.O. Moozhikkara, Kodiyeri, Thalassery, Kannur, Kerala, India

Abstract

Background: Cytoreductive Surgery (CRS) and Hyperthermic Intraperitoneal Chemotherapy (HIPEC) has emerged as the treatment of choice for patients with peritoneal carcinomatosis. The surgery is associated with massive blood and fluid loss resulting in transfusion of intravenous fluids and blood products which can lead to alterations in normal coagulation cascade and can lead to coagulation abnormalities.

Aim of study: Our study aims to find out the incidence of postoperative coagulopathy and factors contributing to it. We also aim to find out the incidence of postoperative thromboembolic complications.

Materials and methods: Data of 43 patients who underwent CRS and HIPEC was collected from hospital medical records and was analyzed retrospectively. The primary outcome of our study was the incidence of postoperative coagulopathy. Abnormal coagulation was defined as platelet count less than 1 lakh/mm3, INR >1.5 and APTT> 45 sec. We recorded the coagulation profile the day before surgery, on the day of surgery and for the first five postoperative days. Details were collected about postoperative transfusion, occurrence of thromboembolic complications and mortality in the first 30 days after surgery.

Result: 60% of the patients (26/43) developed coagulopathy perioperatively. ASA status of the patient, primary disease, postoperative transfusion and delta temperature had significant association with occurrence of postoperative coagulopathy. Greatest reduction in platelet count from preoperative value was on POD-3 with median value of 1.51 (IQR 0.52). Highest increase in INR was on POD-2 (median value of 1.45 (IQR 0.320)) and APTT was on POD-2 (median value of 40(IQR 10) seconds.

Conclusion: The incidence of perioperative coagulopathy after CRS and HIPEC was very high in our study. ASA score, primary disease and delta temperature had significant association with development of postoperative coagulopathy. 9.3% of patients developed symptomatic thromboembolic complications in the first 30 days after CRS and HIPEC.

Key Words: cytoreductive surgery, hyperthermic intraperitoneal chemotherapy, coagulopathy

Address for correspondence:
Dr. Joona Prabhakaran, MBBS, MD Anaesthesiology, Assistant professor, Department of onco-anaesthesiology, Malabar cancer centre, P.O. Moozhikkara, Kodiyeri, Thalassery, Kannur, Kerala, India, Email: drjoonap@gmail.com

Word count: 2710 **Tables:** 05 **Figures:** 03 **References:** 20

Received: 11 November, 2023, Manuscript No. OAR-23-119880
Editor assigned: 12 November, 2023, Pre-QC No. OAR-23-119880 (PQ)
Reviewed: 25 November, 2023, QC No. OAR-23-119880 (Q)
Revised: 03 December, 2023, Manuscript No. OAR-23-119880 (R)
Published: 15 December, 2023, Invoice No. OAR-23-119880

INTRODUCTION

Peritoneal carcinomatosis was previously considered as a terminal stage of certain organ based malignancies and patients were treated with a palliative intent [1]. But recently, Cytoreductive Surgery (CRS) and Hyperthermic Intraperitoneal Chemotherap y (HIPEC) has emerged as the treatment of choice for these patients and have shown mortality benefit in selected patients [2, 3]. Due to the promising mortality benefits, number of patients undergoing CRS and HIPEC is on rise [1, 4-11].

CRS involves macroscopic tumor resection, almost complete removal of the peritoneum, multiorgan resection and variable number of intestinal anastomosis. This is followed by perfusion of heated chemotherapy inside the abdominal cavity [12-14]. Extensive resection associated with CRS alters the capillary permeability and causes widespread tissue damage and massive fluid shift. This is accelerated by vasodilatation caused by neuraxial block and heated chemotherapy [14]. The surgery is associated with massive blood and fluid loss resulting in transfusion of intravenous fluids and blood products. Massive transfusion can induce hypothermia whereas patient is subjected to hyperthermic insult during HIPEC. All these can lead to alterations in normal coagulation cascade and can lead to coagulation abnormalities in the postoperative period. Cancer as such is a risk factor for thromboembolism. Altered

coagulation after CRS and HIPEC can accelerate this [15, 16].

Our study aims to find out the incidence of postoperative coagulopathy and factors contributing to it. We also aim to find out the incidence of postoperative thromboembolic complications.

METHODOLOGY

Data of 43 patients who underwent CRS and HIPEC from September 2018 to June 2023 in our institute, a tertiary cancer center was collected from hospital medical records and was analysed retrospectively. The study was conducted after getting approval from the institutional review board. Our study followed the guidelines of the Declaration of Helsinki. We included all patients more than 18 years who underwent CRS and HIPEC in our center. Patients who underwent staged procedures, emergency re-explorations and those with incomplete medical records were excluded from the study.

The primary outcome of our study was the incidence of postoperative coagulopathy. Abnormal coagulation was defined as platelet count less than 1 lakh/mm3, International Normalized Ratio (INR)>1.5 and Activated Partial Thromboplastin Time (APTT) > 45 seconds. For the same day, if more than one value was available, the most abnormal value was taken for the study. We recorded the coagulation profile the day before surgery, on the day of surgery and for the first five postoperative days. Demographic details like age, sex, American Society Of Anaesthesiologist (ASA) score, comorbidities, height and weight of the patients were recorded. Previous history of any thromboembolic diseases, history of taking anticoagulants and antiplatelet drugs, primary disease and Peritoneal Cancer Index (PCI) score were recorded. Intraoperative details like chemotherapy drug used, delta temperature, dwell time, blood loss, transfusion details and duration of surgery were recorded. Details were collected about postoperative transfusion and mortality in the first 30 days after surgery. Secondary aim of our study was to find out the incidence of thromboembolic complications in the first thirty days after surgery.

Statistical analysis was performed using Statistical Package for the Social Sciences software version 20 (IBM corporation). Mean, median, percentage, and range were used to represent descriptive statistics. Odds Ratios (OR) and corresponding 95% Confidence Intervals (CI) were calculated and statistical significance was defined at as $p<0.05$.

RESULTS

Our study retrospectively analyzed the data of 43 patients. Mean age of the study population was 47 years. Majority of patients were females (37/43), belonged to ASA 2 (29/43). Out of the 43 patients studied, 20 patients had one or more comorbidities and most common comorbidities were hypertension and diabetes.

Out of the 43 patients, 4 patients were taking anticoagulants or antiplatelet drugs preoperatively. Four patients had history of previous thromboembolism. Ovarian carcinoma was the most common primary disease and majority of patients had a PCI score <10. (Table 1 and Table 2) shows the demographic and preoperative data of patients undergoing CRS and HIPEC.

Tab.1. CRS and HIPEC demographic factors

Serial no.	Demographic Factors	Count
1	Age	47
2	Gender (Male:Female)	06:37
3	ASA 1/2/3	13/29/1
4	**Comorbidity**	
	Nil	13
	Hypertension	12
	Diabetes	12
	Thyroid	4
	IHD	4
	CVA	1
	CKD	1

ASA: American Society of Anaesthesiologist,
IHD: Ischemic Heart Disease,
CVA: Cerebral Vascular Accident,
CKD: Chronic Kidney Disease,
PCI: Peritoneal Cancer Index,
HAMN: High Grade Appendiceal Mucinous Neoplasm

Tab.2. CRS and HIPEC preoperative data

SL NO.	Pre-operative data	
1	**Primary disease**	
	Ovary	21
	Colon	6
	Hamn	8

Majority of the surgery lasted 8-10 hours. Out of 43 patients, 18 had a blood loss of 1-2 l. Only 10 patients had a blood loss of >2 litres. 32 patients required PRBC transfusion intra-operatively. Majority of patients had transfusion of 1-2 PRBCS. Only 14 patients needed FFP and 9 needed transfusion of platelets intraoperatively.

22 out of 43 patients received 10-20 crystalloids during the procedure. Out of 43 patients, 34 needed colloids and 25 of them received 1-2 units and 9 required >2 units of hydroxyl ethyl starch in the intraoperative period. Cisplatin and mitomycin were the two chemotherapy drugs used for HIPEC and 23 patients were given cisplatin and 20 were give mitomycin. (Table 3) highlights the intraoperative data of the study population. Majority of the patients had a dwell time of 60 minutes (39/43). One patient had 45 minutes and 3 patients had 90 minutes dwell time.

Tab.3. CRS and HIPEC intraoperative variables

Sl no	Intraoperative variables	Count
1	**Duration of Surgery**	
	8 hours	8
	8-10 hours	27
	>10 hours	8
2	**Blood Loss**	
	<1litre	15
	1-2 litre	18
	>2litre	10
3	**PRC Transfusion**	
	NIL	11
	<2	18
	02-Apr	9
	>4	5
4	**FFP**	
	NIL	29
	<2	3
	02-Apr	3
	>4	8
5	**Platelet**	
	NIL	34
	<2	2
	02-Apr	2
	>4	5
6	**Crystalloid**	
	<10	19
	Oct-20	22
	>20	2
7	**Colloid**	
	NIL	9
	<2	25
	>2	9
8	**Chemotherapy**	
	CISPLATIN	23
	MITOMYCIN	20
9	**DWELL Time**	
	45 minutes	1
	1 hour	39
	90 minutes	3

In the postoperative period, 79% (34/43) of patients needed transfusion of blood products. The incidence of symptomatic thromboembolism was 9.3% in our study. In the first 30 postoperative days, 3 patients had deep vein thrombosis and one patient had pulmonary embolism. 30 day mortality was 4.65%.

60% of the patients (26/43) developed coagulopathy (platelet count<1 lakh/mm^3, INR>1.5, APTT>45 seconds) perioperatively.

Statistically significant difference was found between preoperative platelet count and platelet count evaluated on POD 0 through POD 5. Greatest reduction in platelet count from preoperative value (2.68: IQR-1.19) was on POD-3 (median difference-1.145 with 95%CI -1.300 to-0.905) with median value of 1.51 (IQR 0.52). Platelet count recovered to 1.67 by POD-5.

Preoperative median INR was 1.01(0.08). Highest increase in INR from preoperative

value was on POD-2 (median difference of 0.395 with 95% CI 0.335-0.460) with a median value of 1.45 (IQR 0.320. Difference between preoperative INR and INR values on POD-0 through POD-5 was also statistically significant. INR values came down to a median of 1.09 (IQR 0.10) by POD-5.

Median preoperative APTT was 26.6 seconds (IQR 7.0). Greatest increase in APTT was on POD-2 (12.875: IQR 10.45-15.5). On POD-2, median APTT was 40(IQR 10) seconds which came down to 30 seconds on POD-5. There was statistically significant difference between preoperative APTT values and APTT values collected on POD0 through POD-5. (Table 4 and Table 5) shows the trend in platelet count, INR and APTT values on preoperative day and POD 0 through POD 5 and the difference between preoperative values and postoperative values.

Tab.4. Preoperative and postoperative coagulation metrics

Measurement	platelets		INR		APTT	
	Median(IQR)	Min - max	Median(IQR)	Min - max	Median(IQR)	Min - max
Pre-op	2.68(1.19)	0.99-7.04	1.01 (0.08)	0.84-1.29	26.6 (7.O)	21-35
POD 0	2.20 (1.17)	0.8-4.19	1.28 (0.15)	1.04-1.68	33.10 (8.40)	24-43
POD 1	1.87 (0.79)	0.98-3.08	1.36 (0.29)	1.05-1.94	36.8 (5.90)	28.5-48.6
POD 2	1.62 (0.56)	0.84-3.45	1.45 (0.32)	1.06-2.78	40.00 (10)	28-62
POD 3	1.51 (0.52)	0.84-2.1	1.28 (0.27)	1.0-2.12	37 (10)	27-62
POD 4	1.62 (0.65)	0.95-4.5	1.20 (0.25)	0.99-2.14	35 (11.30)	22-68
POD 5	1.67 (0.65)	0.78-4.24	1.09 (0.10)	0.94-4.96	30 (10)	1- 72

INR: International Normalized Ratio,
APTT: Activated Partial Thromboplastin Time,
IQR: Inter Quartile Range

Tab.5. Preoperative versus postoperative coagulation metrics

comparison	platelet		INR		APTT	
	Median difference	95% CI median difference	Median difference	95% CI Median difference	Median difference	95% CI Median difference
Pre op-POD 0	-0.51	-0.720 to -0.350	0.245	0.185 to 0.285	5.385	4.220 to 6.50
Pre op-POD 1	-0.765	-0.575 to -0.575	0	to 0.380	5	11.080
Pre op-POD 2	-1.01	-1.205 to -0.840	0.395	0.335 to 0.460	12.875	10.45 to 15.5
Pre op-POD 3	-1.145	-1.360 to -0.905	0.255	0.190 to 0.335	9.602	6.935 to 12.10
Pre op-POD 4	-1.035	-1.260 to -0.770	0.155	0.100 to 0.220	6.675	4.30 to 9.12
Pre op-POD 5	-0.82	-1.060 to -0.595	0.055	0.020 to 0.090	2.6	0.60 to 5.20

INR: International Normalized Ratio,
APTT: Activated Partial Thromboplastin Time,
CI: Confidence Interval,
POD: Postoperative Day

The following graphs shows the trend in platelet count, INR and APTT values in the preoperative and first five postoperative days (Figure 1-3).

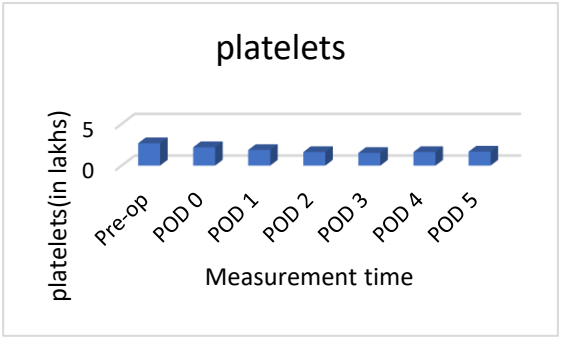

Fig.1. Trend in platelet count (Platelet count in lakh/mm3 , POD: postoperative day)

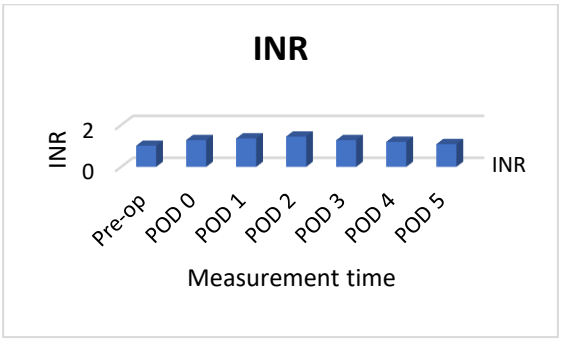

Fig.2. Trend in INR

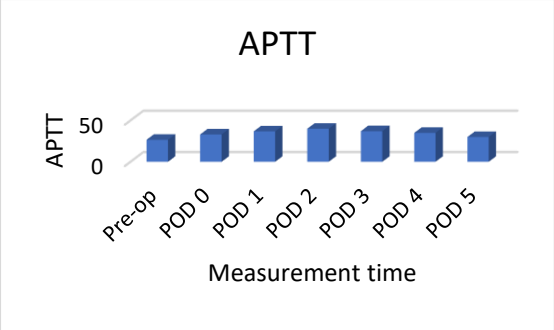

Fig.3. Trend in APTT(APTT in seconds)

We analysed the perioperative variables which have significant association with the development of coagulopathy. Age, sex and presence of comorbidities have no significant association. ASA status has significant association with coagulopathy. Out of 26 patients who developed postoperative coagulopathy, 21 belonged to ASA 2, 4 in ASA 1 and one patient belonged to ASA 1. Out of 4 patients who were on antiplatelets or anticoagulants three developed coagulopathy. 3 out of 4 patients who had previous history of thromboembolism developed coagulopathy. But these variables had no significant association.

We found significant association between primary disease and coagulopathy. Out of 26 patients who developed coagulopathy, 9 had ovarian carcinoma, 7 had high grade mucinous neoplasm of appendix and 7 had pseudomyxoma peritonei. We couldn't find any significant association with type of chemotherapy drug, dwell time and PCI score.

Out of 28 patients who had >1 litre blood loss, 20 developed coagulopathy, but the association was not significant. Our study couldn't find any significant association between development of coagulopathy and transfusion of crystalloids, colloids, blood products and duration of surgery. There was significant association between coagulopathy and postoperative transfusion of blood products. Out of 34 patients who received postoperative transfusion, 25 had coagulopathy.

There was no significant association between coagulopathy and occurrence of symptomatic thromboembolism or 30 day mortality postoperatively.

Median delta temperature was 60C with IQR of 10C. Delta temperature had significant association with occurrence of postoperative coagulopathy.

DISCUSSION

According to our study, 60% of patients who underwent CRS and HIPEC developed coagulopathy in the first five postoperative days. The etiology of coagulopathy can be multifactorial [1].
Median platelet count came down to reach a nadir of 1.51 on POD-3 after which it started rising to reach a value of 1.67 on POD-5. INR and APTT had an increasing trend to reach a maximum value on POD 2(1.45 and 40seconds) and it gradually decreased to become normal by POD 5(1.09 and 30 seconds). This indicates that there is increased risk of bleeding related complications in the first few postoperative days(15) after which coagulation profile gradually normalizes.

Dranchnikov et al showed that fibrinogen and D-dimer values show a rising trend after POD-5 which indicates that there is increased risk of thromboembolic complications after POD-5. Though our study doesn't analyse the D-dimer or fibrinogen values, all four patients (out of 43) who developed thromboembolic complications had their symptoms during the second postoperative week.

In our study, 9.3% of patients developed thromboembolic complications within one month after CRS and HIEC. Compared to previous studies, this percentage is in the middle range (3-14%)[17-20]. According to Dranchnikov et al, only 6% of patients had thromboembolic complications in the first six months after surgery.

Eventhough the incidence of coagulopathy was high in the postoperative period in patients with PCI>30, those on preoperative anticoagulants, those with more than one litre blood loss, those who received more than two blood products or colloids, the association was not statistically significant. ASA score, delta temperature, primary disease and postoperative transfusion of blood products were the perioperative variables having significant association with coagulopathy according to our study. This

was in contrast to the results of Hurdle et al who found that only intraoperative transfusion of RBCs had significant influence on the occurrence of postoperative coagulopathy [1].

There were several limitations to our study. Sample size of study population was small. Since this is a retrospective study, extensive data about D-dimer, fibrinogen and thromboelastogram were not available for all patients from the medical records. Hence these parameters couldn't be analysed. Patients were followed up only for one month postoperatively. Hence delayed thromboembolic complications couldn't be analysed. Due to this, the incidence of thromboembolic complications obtained from our study may not represent the actual burden of the problem. Further prospective studies are needed to evaluate the trend of procoagulant factors in the postoperative period to analyse the possibility of thromboembolic complications.

CONCLUSION

The incidence of perioperative coagulopathy after CRS and HIPEC was very high after CRS and HIPEC in our study. ASA score, primary disease and delta temperature had significant association with development of postoperative coagulopathy. In majority of patients, coagulation profile came down to almost normal range by fifth day after surgery. But vigilant postoperative monitoring is required for early detection of coagulopathy and for avoiding complications. 9.3% of patients developed symptomatic thromboembolic complications in the first 30 days after CRS and HIPEC.

ACKNOWLEDGMENT

Nil.

FUNDING

Nil.

REFERENCES

1. Hurdle H, Bishop G, Walker A, Moazeni A, Paloucci EO, et al. Coagulation after cytoreductive surgery and hyperthermic intraperitoneal chemotherapy: a retrospective cohort analysis. Can J Anaesth. 2017;64:1144-1152.
2. Witkamp AJ, de Bree E, Van Goethem R, Zoetmulder FA. Rationale and techniques of intra-operative hyperthermic intraperitoneal chemotherapy. Cancer treat rev. 200;27:365-374.
3. Roviello F, Caruso S, Marrelli D, Pedrazzani C, Neri A, et al. Treatment of peritoneal carcinomatosis with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy: state of the art and future developments. Surg oncol. 2011;20:38-54.
4. Pintado MC, Lasa Unzue I, Gómez Sanz R, Diez Alonso M, Ortega MA, et al. Hematological Alterations after Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy. J Clin Med. 2023;12:4323.
5. Yan TD, Welch L, Black D, Sugarbaker PH. A systematic review on the efficacy of cytoreductive surgery combined with perioperative intraperitoneal chemotherapy for diffuse malignancy peritoneal mesothelioma. Ann Oncol. 2007;18:827-834.
6. Yan TD, Black D, Savady R, Sugarbaker PH. A systematic review on the efficacy of cytoreductive surgery and perioperative intraperitoneal chemotherapy for pseudomyxoma peritonei. Ann surg oncol. 2007;14:484-492.
7. Yan TD, Black D, Savady R, Sugarbaker PH. Systematic review on the efficacy of cytoreductive surgery combined with perioperative intraperitoneal chemotherapy for peritoneal carcinomatosis from colorectal carcinoma. J Clin Oncol. 2006;24:4011-4019.
8. Yan TD, Black D, Sugarbaker PH, Zhu J, Yonemura Y, et al. A systematic review and meta-analysis of the randomized controlled trials on adjuvant intraperitoneal chemotherapy for resectable gastric cancer. Ann surg oncol. 2007:2702-2713.
9. Bijelic L, Jonson A, Sugarbaker PH. Systematic review of cytoreductive surgery and heated intraoperative intraperitoneal chemotherapy for treatment of peritoneal carcinomatosis in primary and recurrent ovarian cancer. Ann Oncol. 2007;18:1943-1950.
10. Glehen O, Kwiatkowski F, Sugarbaker PH, Elias D, Levine EA, et al. Cytoreductive surgery combined with perioperative intraperitoneal chemotherapy for the management of peritoneal carcinomatosis from colorectal cancer: a multi-institutional study. J Clin Oncol. 2004;22:3284-3292.
11. Verwaal VJ, Bruin S, Boot H, Van Slooten G, Van Tinteren H. 8-year follow-up of randomized trial: cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy in patients with peritoneal carcinomatosis of colorectal cancer. Ann surg oncol. 2008;15:2426-2432.
12. Sugarbaker PH. Peritonectomy procedures. Ann surg. 1995;221:29.
13. Esquivel J, Sticca R, Sugarbaker P, Levine E, Yan TD, et al. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in the management of peritoneal surface malignancies of colonic origin: a consensus statement. Ann surg oncol. 2007;14:128-133.
14. Gupta R, Gupta N, Sirohiya P, Pandit A, Ratre BK, et al. Perioperative anaesthetic management in cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC): a retrospective analysis in a single tertiary care cancer centre. Pleura Peritoneum. 2022;7:127-134.
15. Dranichnikov P, Mahteme H, Cashin PH, Graf W. Coagulopathy and venous thromboembolic events following cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. Ann Surg Oncol. 2021:1-1.
16. Araña LF, Fuentes-García D, Calvo MJ, Hernández-Palazón J, Martínez JG, et al. Alterations in hemostasis during cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in patients with peritoneal carcinomatosis. Cir Esp (Engl Ed). 2015;93:496-501.
17. Bartlett EK, Meise C, Roses RE, Fraker DL, Kelz RR, et al. Morbidity and mortality of cytoreduction with intraperitoneal chemotherapy: outcomes from the ACS NSQIP database. Ann surg oncol. 2014;21:1494-1500.
18. Lanuke K, Mack LA, Temple WJ. A prospective evaluation of venous thromboembolism in patients

undergoing cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. Can J Surg. 2009;52:18.
19. Baumgartner JM, Kwong TG, Ma GL, Messer K, Kelly KJ, et al. A novel tool for predicting major complications after cytoreductive surgery with hyperthermic intraperitoneal chemotherapy. Ann surg oncol. 2016;23:1609-1617.
20. Rottenstreich A, Kalish Y, Kleinstern G, Yaacov AB, Dux J, et al. Factors associated with thromboembolic events following cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. J Surg Oncol. 2017;116:914-920.