ORIGINAL ARTICLE

Thromboembolic Complications in Patients with Digestive Malignancies

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Abstract. Introduction. *Venous thromboembolism is the second leading cause of mortality in cancer patients. Patients with malignant conditions have a ninefold increased risk of thrombotic complications, and approximately 20% of patients with venous thromboembolism also associate cancer. The aim of our study was to determine the incidence and predictive factors for thromboembolic complications in patients with digestive cancers. Materials and methods: We conducted a retrospective study over six years, including 200 patients hospitalized in the Clinical Emergency Hospital of Bucharest, Romania, with digestive malignancies and thromboembolic complications. Results: The prevalence of venous thromboembolism among patients with malignant digestive tumors was 9.2%. The average age of these patients was 66 years. The malignancies with the highest incidence of thrombotic complications were pancreatic cancer, colorectal cancer, hepatocellular carcinoma, and gastric cancer. Histologically, all cancers were identified as adenocarcinoma, with 70% of patients exhibiting poorly differentiated tumors, and advanced tumor stages were observed in all cases. The most prevalent thrombotic complication was portal vein thrombosis, followed by deep vein thrombosis and pulmonary thromboembolism. The in-hospital mortality rate of these patients was 23.5%, while the 5-year mortality rate was 82.5%. Conclusions: We propose, as a future research direction, the enhancement of approaches to evaluate the risk of venous thromboembolism and discovery of novel biomarkers with a predictive role in patients with malignant tumors.*

Keywords*: venous thromboembolism; digestive cancers; prevalence; risk factors; mortality rate; prognosis.*

1. INTRODUCTION

Armand Trousseau first described the association between cancer and thrombosis in 1865 [1,2]. He identified thrombophlebitis in patients with malignant neoplasms, suggesting that the occurrence of thrombotic complications is due to changes in hemostasis [1,2]. Trousseau syndrome is named after the French physician, who ironically noted the occurrence of thrombophlebitis before his death from gastric cancer [1,2]. The correlation of cancer with thrombotic phenomena was also reported by Jean Baptiste Bouillaud in 1823 [1,2]. The procoagulant status of malignant neoplasms is still being investigated today [1,2].

Sudden death following a first episode of thromboembolism, asymptomatic cases that remain undiagnosed, or accidental discovery are factors that make it difficult to pinpoint the exact epidemiology of thromboembolism. However, it is well known that pulmonary embolism is the third most common cardiovascular disease and cause of cardiovascular death, being

preceded by myocardial infarction and stroke [3]. The 2019 European Society of Cardiology (ESC) guidelines specified an incidence of pulmonary thromboembolism (PTE) between 39-115 cases per 100.000 population and deep deep vein thrombosis (DVT) between 53-162 cases per 100.000 population [3-5]. Although data on the involvement of ethnicity in the occurrence of venous thromboembolism (VTE) are relatively scarce, studies have shown that Caucasian populations are less likely to develop VTE than African American populations. The prevalence of venous thromboembolic disease is lower in Asian and Hispanic populations compared to Caucasians [4,5].

The incidence of VTE increases with age for both men and women [4]. Studies have shown that the incidence of VTE is 8 times higher in patients aged > 80 years compared to those in the fifth decade of life [3]. Also, the risk of VTE increases from 1/10,000 at birth to 1/100 in individuals aged > 80 years [6]. Patients aged > 40 years are much more likely to develop thrombotic events. With each decade of life, the risk of developing VTE in these patients will become approximately twice as high [7].

VTE is more common in women during childbearing years. Subsequently, after the age of 45 years, the incidence rate of VTE is higher in men [4]. The incidence of VTE increases further during pregnancy. Thus, while the overall incidence of VTE has been estimated at around 200 cases per 100,000 women, the risk of developing VTE is four times higher in pregnant women than in fertile women of the same age [4]. The postpartum period is also associated with a five times higher risk of developing thrombotic events than the pregnancy period [4]. VTE is considered a chronic disease, with the possibility of recurrent episodes [4]. The risk of developing a new episode of VTE has been shown to be highest in the first 6-12 months after initial diagnosis [4]. Male gender, advanced age, patients with active cancer, and neurological diseases with associated paralysis are some of the factors that may influence VTE recurrence [4].

The major complications of VTE are postthrombotic syndrome and chronic thromboembolic pulmonary hypertension. The patients with a history of VTE have a 17-fold increased risk of developing post-thrombotic syndrome, and VTE is the cause of 12% of all cases of post-thrombotic syndrome in the US [4]. Thromboembolic pulmonary hypertension has an incidence of 6.5 million cases annually [4]. The survival following VTE differs, with pulmonary embolism being a negative predictor. The patients with DVT have an 18-fold lower risk of death compared with those with PTE, who in a quarter of cases present clinically with sudden death [4].

The increased incidence of thromboembolic events varies according to tumor location, histopathologic type, stage of cancer, oncologic treatment, presence or absence of metastases and associated comorbidities. Most studies show a particular importance of the primary tumor location in the development of venous thrombosis, with the highest risk in patients with pancreatic, lung, gastric, ovarian and malignant brain tumors [8].

Cancer is responsible for about 20% of VTE. A study conducted between 1979 and 1999 found that the occurrence of thromboembolic complications was twice as common in patients with cancer compared to those without malignant neoplasms [9]. Venous thrombosis is also the second leading cause of death in cancer patients [2].

2. THE OBJECTIVE OF THE STUDY

We conducted a retrospective, observational study in the Clinical Emergency Hospital of Bucharest, Romania. The aim of this study was to identify the prevalence of thromboembolic complications and some predictors of thromboembolic complications among patients with digestive malignancies.

The secondary objectives include:

1. Evaluation of the frequency of digestive cancers and thromboembolic complications, according to localization.

2. Evaluation of digestive cancers in terms of tumor stage, histologic type and degree of differentiation.
3. Assessment of the correlation between the type of digestive malignant neoplasm and the type of thromboembolic event.
4. Identification of risk factors for thromboembolic complications in patients with digestive cancers.
5. Analyzing the relationship between the most common comorbidities of patients with digestive cancers and the occurrence of VTE.
6. Analysis of the influence of surgical treatment, chemotherapy and radiotherapy on the risk of thromboembolic complications.
7. Evaluation of the association of infectious complications with VTE in our study group.
8. Evaluation of mortality rate and length of hospitalization in our study group.

3. MATERIALS AND METHODS

We conducted a retrospective, observational study, in which we included 200 patients with digestive malignant neoplasms, hospitalized in the Clinical Emergency Hospital of Bucharest, Romania, between January 2018 and January 2024.

We obtained the approval of the Ethics Committee of the hospital (approval no. 799/ 29.01.2024). The patients enrolled in the study signed an informed consent giving their agreement to participate.

The inclusion criteria were:

- Patients diagnosed with digestive malignancies who have developed thromboembolic complications.

The exclusion criteria were:

- Patients diagnosed with malignant neoplasms other than digestive malignancies.
- Patients with digestive cancers without associated thromboembolic complications.

The variables followed in the study were age, sex, smoking, diagnosis of digestive cancer and VTE, histopathologic type, degree of differentiation and tumor stage, treatment of the patient prior to admission for thromboembolic complications, associated comorbidities, length of hospitalization, and mortality rate.

Data were collected from the database of the hospital. They were initially entered into an Excel database. Later, for statistical analysis, we used the Microsoft Excel program. The results were presented graphically in the form of tables and figures.

4. RESULTS

The prevalence of VTE among patients with malignant digestive tumors was 9.2%. We started the statistical analysis with the evaluation of some epidemiological parameters, such as gender and age of the patients included in the study. Regarding the distribution of patients by sex, we observed a predominance of males (60%, 120 patients) compared to females (40%, 80 patients) (Figure 1).

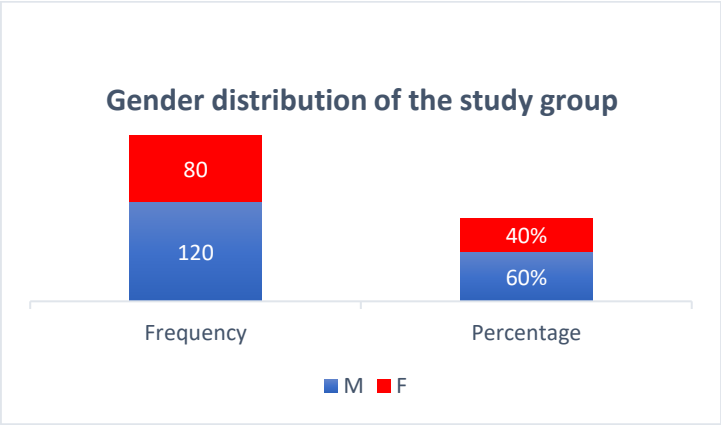

Figure 1. Gender distribution of the study group.

The age of the patients included in our study ranged from 31 to 92 years, with an average age of 66 years. Most patients with associated VTE (78 patients) were in the sixth decade of life (Figure 2).

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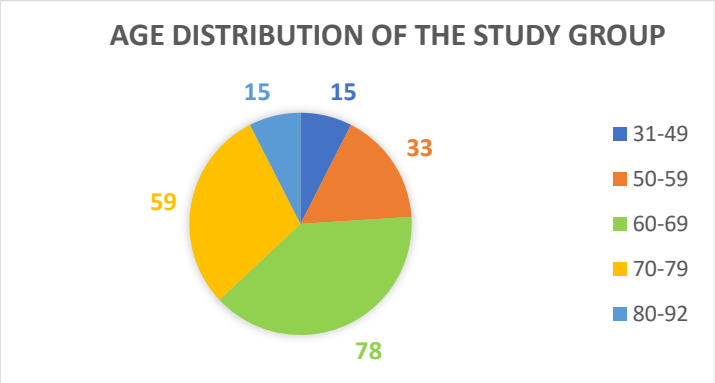

Figure 2. Age distribution of the study group.

Of the total of 200 patients, pancreatic cancer was present in 58 patients (28%), representing the most common malignant neoplasm in our study group (Table 1). It is followed by colorectal cancer, found in 53 patients (26.5%), hepatocarcinoma in 47 patients (23.5%), gastric cancer in 20 patients (10%) and cholangiocarcinoma in 16 patients (8%). Other malignant neoplasms identified were Vaterian ampuloma (1%), esophageal cancer (0.5%) and duodenal cancer (0.5%). One patient associated hepatocarcinoma with sigmoid colon cancer (0.5%) and another hepatocarcinoma with rectal cancer (0.5%) (Table 1).

Regarding the localization of pancreatic cancer, cephalopancreatic tumors predominated, identified in 47 patients (81.03% of all pancreatic tumors). Corporeal pancreatic cancer was present in 6 patients (10.34%) and corporeo-caudal in 2 patients (1%) (Table 1). Only one patient (0.5%) presented with cephalopancreatic and uncinate process cancer (Table 1).

Table 1. Distribution of patients by gastrointestinal cancer localization.

Cancer	Number of patients	Percentage
Cephalopancreatic	47	23.5%
Cephalopancreatic and uncinated process	1	0.5%
Corporeal pancreatic	6	3%
Pancreatic corporal-caudal	2	1%
Pancreatic output	2	1%
Colorectal	53	26.5%
Hepatocarcinoma	47	23.5%
Gastric	20	10%
Cholangiocarcinoma	16	8%
Vaterian ampuloma	2	1%
Esophageal	1	0.5%
Duodenal	1	0.5%
Hepatocarcinoma and sigmoid colon cancer	1	0.5%
Hepatocarcinoma and rectal cancer	1	0.5%

Of the patients included in our study group, 72 patients (36%) were diagnosed with portal vein thrombosis, 51 patients (25.5%) with DVT, 34 patients (17%) with PTE, 11 patients (5.5%) with inferior vena cava thrombosis, 7 patients (3.5%) with splenic vein thrombosis, 5 patients (2.5%) with superior mesenteric vein thrombosis, 3 patients (1.5%) with spleno-mesenteric confluent thrombosis, one patient (0.5%) with porto-mesenteric confluent thrombosis, one patient (0.5%) with right suprahepatic vein thrombosis, one patient (0.5%) with superior vena cava thrombosis, one patient (0.5%) with recto-sigmoid vein thrombosis, and one patient (0.5%) with central retinal vein thrombosis (Figure 3). Also, 12 patients (6%) associated DVT with PTE (Figure 3).

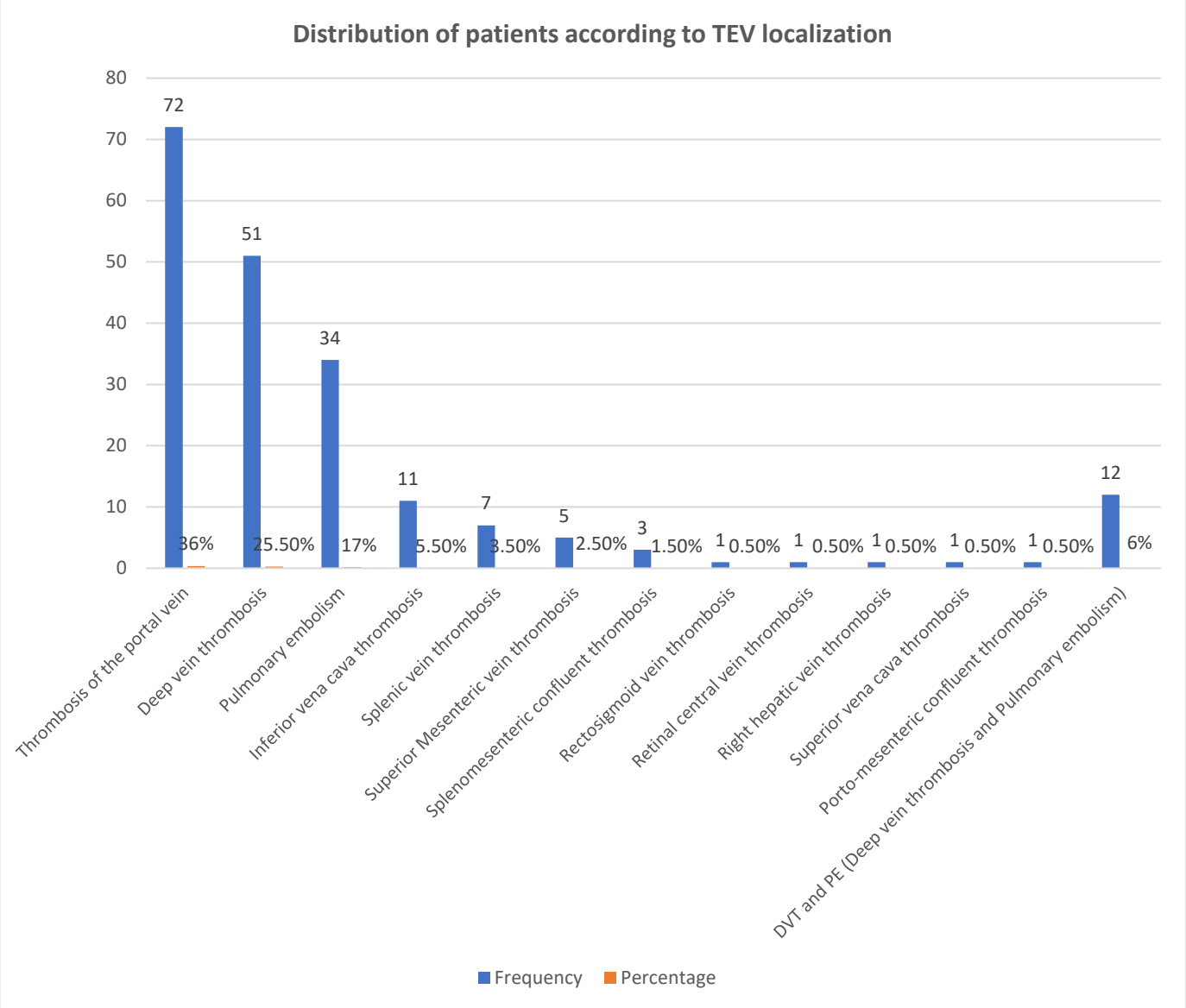

Figure 3. Distribution of patients by VTE localization.

Figure 4 shows the cancers that were complicated by portal vein thrombosis. Of these, the most frequent was hepatocarcinoma. Thus, of the total 47 patients with hepatocarcinoma, 31 patients (65.95%) had associated portal vein thrombosis. Pancreatic cancer ranked second, accounting for 41.37% of cases (24 out of 58 patients) associated with this complication. Portal vein thrombosis was also identified in 9 patients with cholangiocarcinoma, 5 patients with colorectal cancer, 2 patients

with gastric cancer, and in the patient who associated hepatocarcinoma and sigmoid colon cancer (Figure 4).

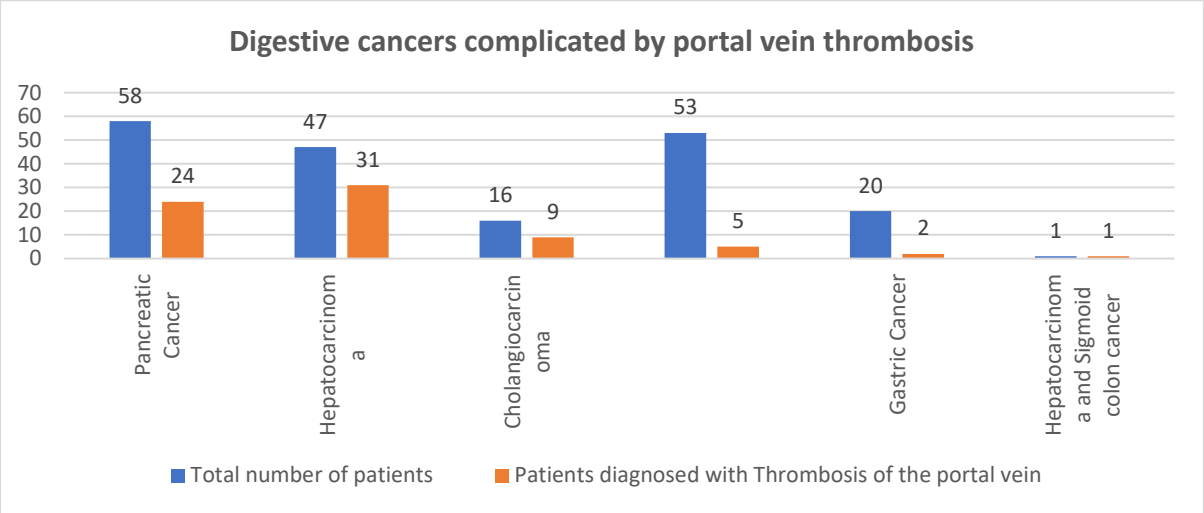

Figure 4. Digestive cancers complicated by portal vein thrombosis.

In terms of DVT, the cancer most frequently associated with this complication was colorectal cancer. Thus, about half of the colorectal cancer patients (26 patients) associated this complication (Figure 5). DVT was also diagnosed in five patients (31.25%) with cholangiocarcinoma, six patients (30%) with gastric cancer, 10 patients (17.24%) with pancreatic cancer and four patients (8.5%) with hepatocarcinoma (Figure 5).

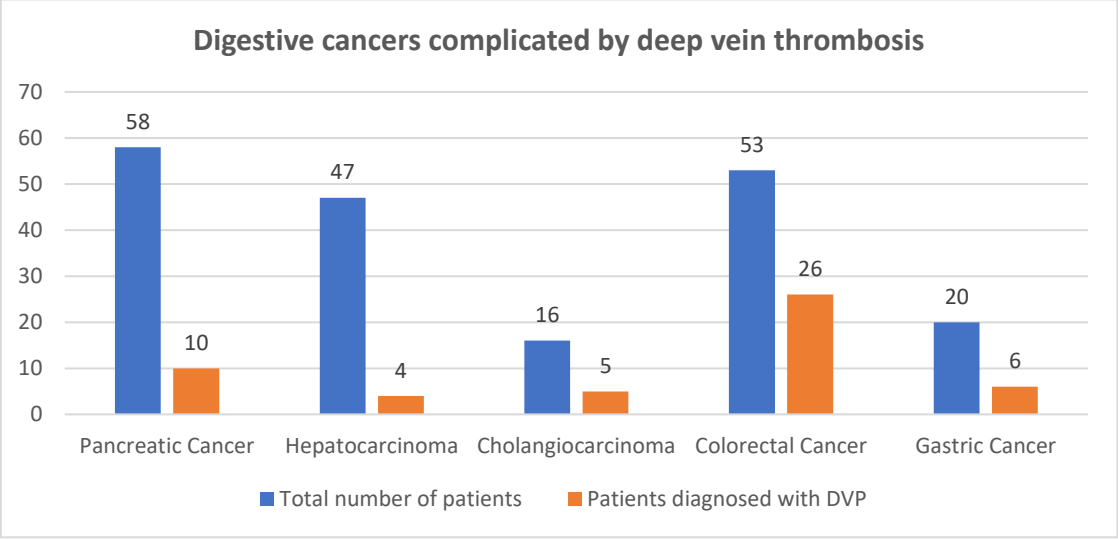

Figure 5. Digestive cancers complicated by deep vein thrombosis.

PTE has been identified in 40% of gastric cancer patients, specifically in 8 out of 20 individuals (Figure 6). PTE was detected in 11 colorectal cancer patients (10.75%), 10 pancreatic cancer patients (17.24%), and three hepatocarcinoma patients (6.38%) (Figure 6). In addition, the sole cases of esophageal cancer and hepatocarcinoma that were linked to rectal cancer in our study each had associated PTE (Figure 6).

Figure 7 shows the frequency of association of DVT and PTE in patients with digestive cancers. We thus observe that of the total cases of patients who associated two thromboembolic complications, 50% were colorectal cancer patients, 17% hepatocarcinoma patients, 17% pancreatic cancer patients, and 16% gastric cancer patients.

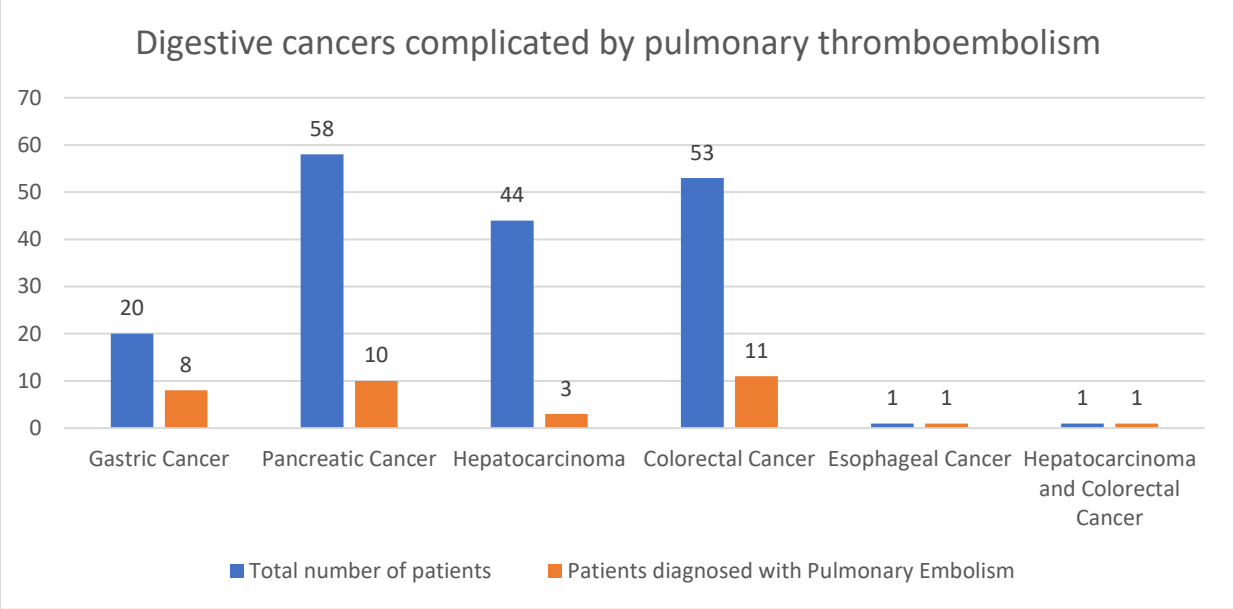

Figure 6. Digestive cancers complicated by PTE.

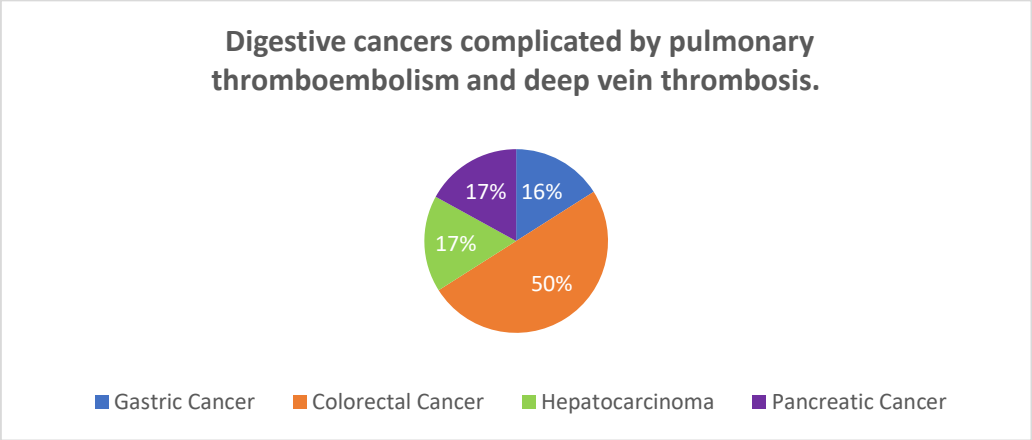

Figure 7. Digestive cancers complicated by PTE and DVT.

Subsequently, we examined the histological diagnosis of the tumors illustrated in Figure 8, their differentiation grade presented in Table 2, and the tumor stage outlined in Table 3. We therefore note the sole occurrence of adenocarcinoma, regardless of the tumor's location. In our study group, pancreatic adenocarcinoma was the predominant cancer type linked to thromboembolic events. The data on differentiation degree and tumor stage was accessible for only a restricted number of patients. It is observed that most patients presented with poorly differentiated tumors, comprising 18 grade 3 and two grade 4 cases, as indicated in Table 2, alongside advanced tumor stages, including 24 patients with stage 4, two patients with stage 3C, and one patient with stage 3B, as detailed in Table 3.

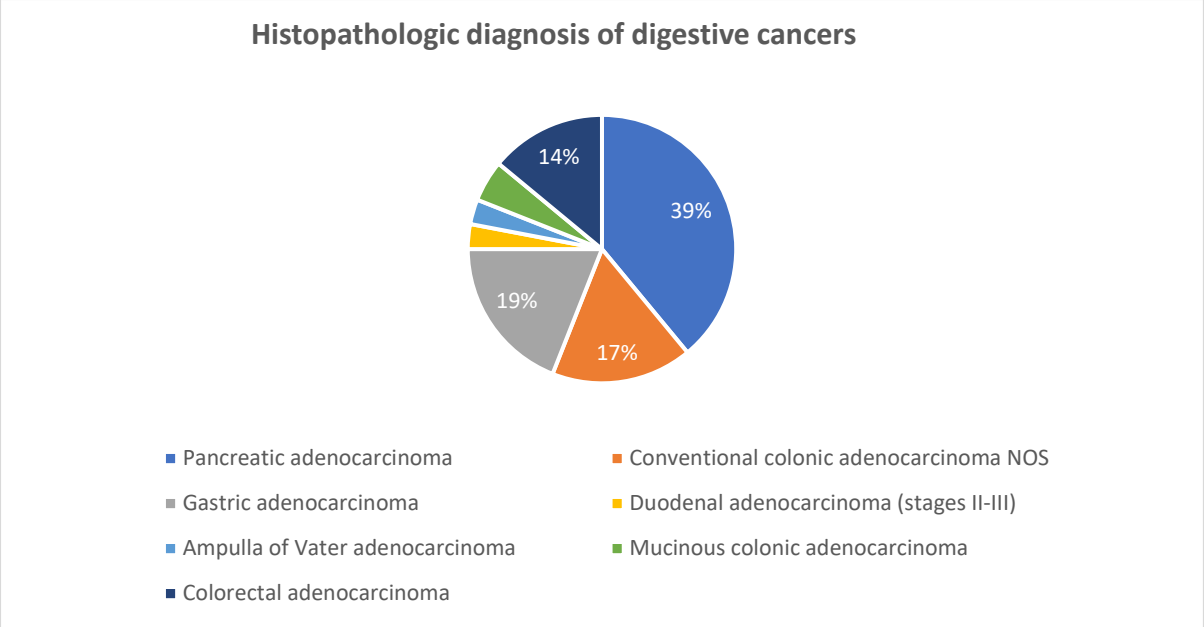

Figure 8. Histopathologic diagnosis of digestive cancers in our study.

Table 2. Degree of tumors differentiation in our study group.

Grade	Frequency	Percentage
1	**2**	**1%**
2	**12**	**6%**
3	**18**	**9%**
4	**2**	**1%**
Unspecified	**166**	**83%**
Total	**200**	**100%**

Table 3. Tumor stage of patients included in our study.

Cancer stage	Frequency	Percentage
3B	1	0.5%
3C	2	1%
4	24	12%
Unspecified	173	86.5%
Total	200	100%

Next, we sought to identify a number of risk factors for thromboembolic complications in patients with digestive cancers. We thus assessed patients' comorbidities, infectious complications, family history, treatment for oncologic pathology (surgery, chemotherapy, radiotherapy), presence of central venous catheter (CVC), smoking, and their impact on thromboembolic risk (Figure 9).

The most frequent comorbidity in patients with digestive cancers and VTE was hypertension, present in 80 of the 200 patients included in our study (40%). This was followed, in order of frequency, by diabetes mellitus (47 patients, 23.5%), atrial fibrillation (30 patients, 15%), renal failure (25 patients, 12.5%), ischemic heart disease (24 patients, 12%), valvular heart disease (22 patients, 11%) and COPD (5 patients, 2.5%) (Figure 9). Also, 53 patients (26.5%) had associated infectious complications, 25 patients (12.5%) were smokers and 14 patients (7%) had CVC.

In terms of oncologic treatment, 70 patients (35%) had undergone surgery prior to the onset of thromboembolic complications, of

whom 27 patients (13.5%) had a recent history of surgery. In addition, 64 patients (32%) had received or were undergoing chemotherapy and 15 patients (7.5%) radiotherapy. Only one patient was on oral contraceptives (OCP) and only one patient had a family history of cancer. No patient had thrombophilia.

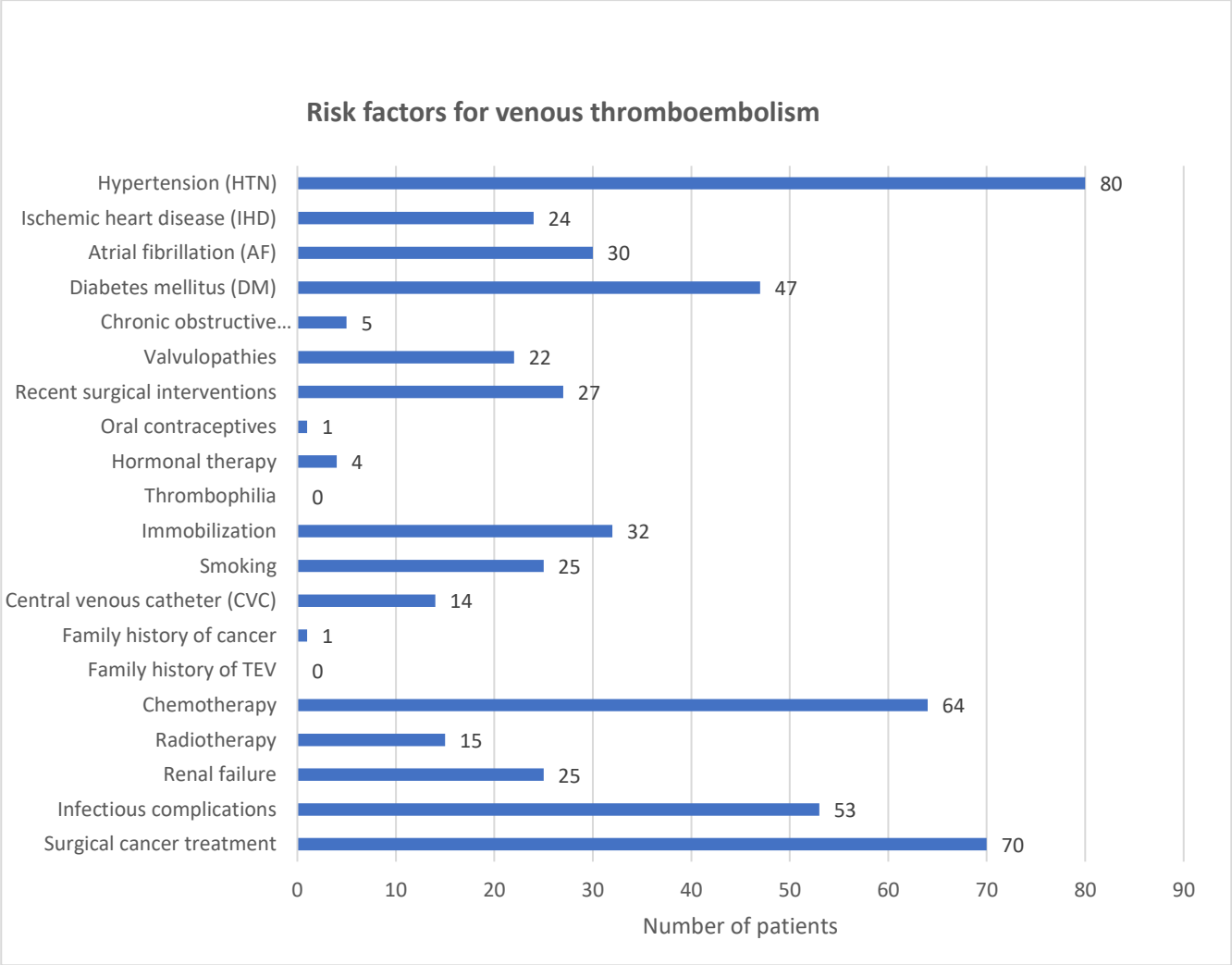

Figure 9. Risk factors for VTE

Hypertension was the most common comorbidity in our study cohort. According to the grade of hypertension, the distribution of patients was as follows: 0.5% (one patient) had grade I, 7% (14 patients) grade II and 8% (16 patients) grade III. Thus, we observe that most patients had associated grade II or grade III hypertension. In conclusion, out of the total of 200 patients, 40% (80 patients) had associated hypertension.

Chemotherapy was reported by 32% (64 patients) of the patients included in our study. The remaining 136 patients either did not receive chemotherapy or this treatment was not mentioned in their discharge. The monochemotherapy treatment followed by patients included Bevacizumab, Capecitabine, Olaparib or Sorafenib. Polychemotherapy included combinations of different drugs: Paclitaxel, Carboplatin and Bevacizumab, Oxaliplatin and Capecitabine, Gemcitabine and Cisplatin, Gemcitabine and Oxaliplatin, Cisplatin and Capecitabine (Figure 10). Bevacizumab therapy was the most used in our study group. Of the total 64 patients who received chemotherapy, 81% (52 patients) did not have the specified chemotherapy regimen.

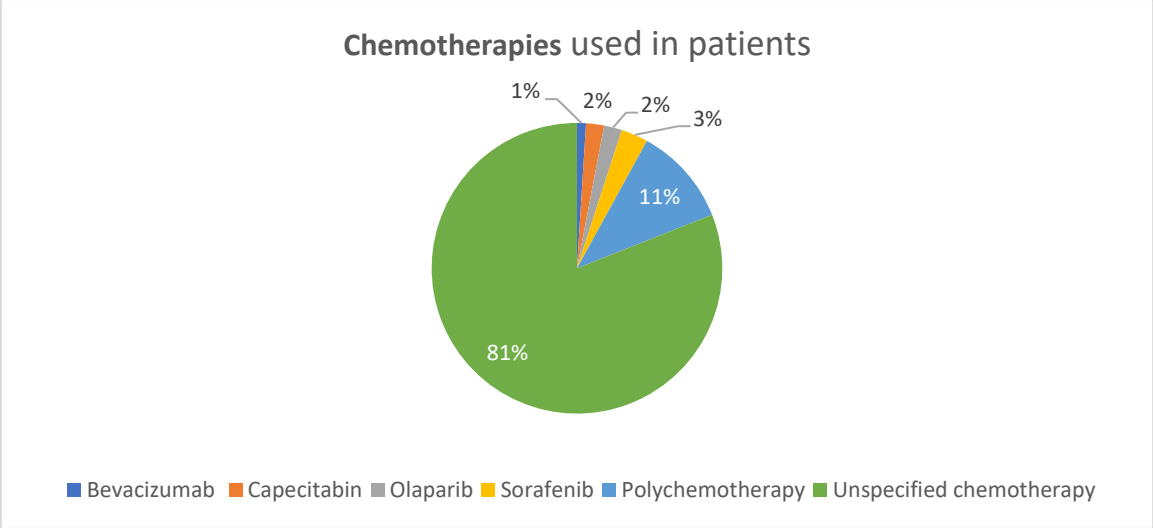

Figure 10. Chemotherapies used in patients in our study group.

The classes of anticoagulant drugs used in our study are, in order of frequency:

- Direct oral anticoagulants (DOACs) - in 20 patients (41%), of which only apixaban and rivaroxaban were used.
- vitamin K antagonists (acenocumarol) - in 11 patients (23%).
- low molecular weight heparins (LMWHs) in 17% of cases (Figure 11).

Also, in 19% of cases, the anticoagulant treatment regimen used for thrombotic complications was not specified.

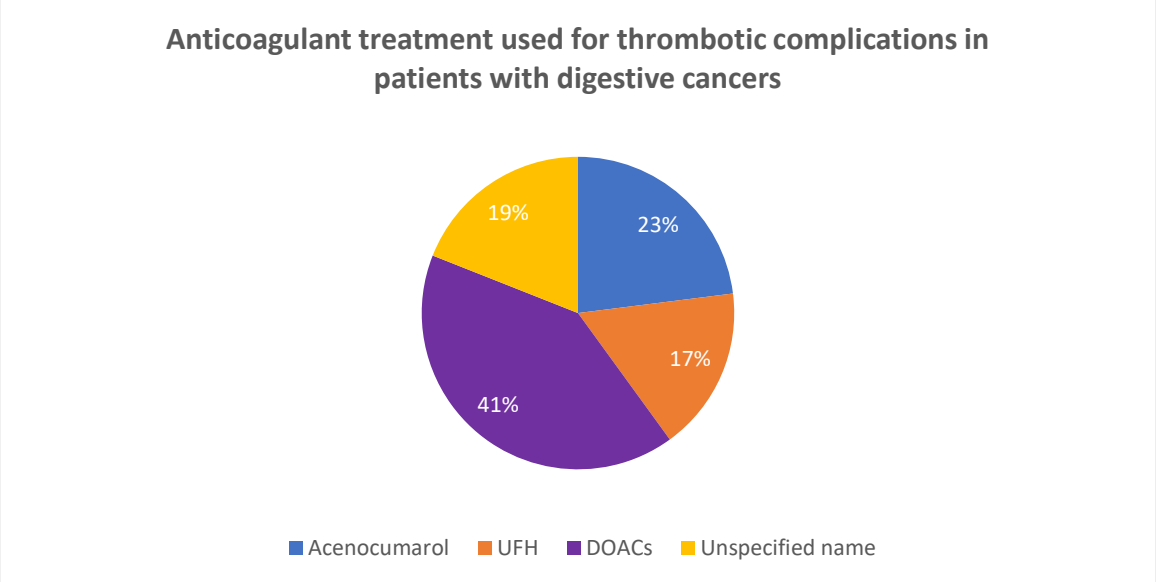

Figure 11. Anticoagulant treatment used for thrombotic complications in patients with digestive cancers.

The in-hospital death rate among patients in our study was 23.5% (47 patients) (Figure 12). Also, 82.5% of these patients have died to date (Figure 13).

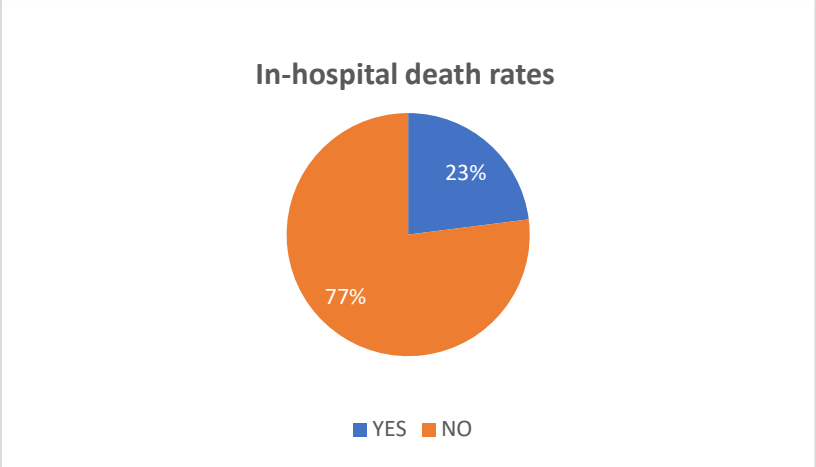

Figure 12. In-hospital death rates.

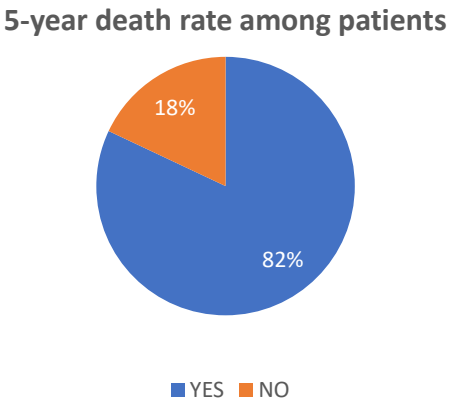

Figure 13. 5-year death rate among patients in our study.

The mean duration of hospitalization of patients with digestive cancers and thromboembolic complications was 155.5 days, with a minimum duration of one day and a maximum duration of 310 days (Table 4).

Table 4. Length of hospitalization of patients included in our study.

Hospital length stay	No. of days
Minimum no. of days	1
Maximum no. of days	310
Average length of hospital stay	155,5

5. DISCUSSION

Our study aimed to investigate the frequency of thromboembolic complications and to identify predictors for these complications among patients with digestive malignancies. Regarding sex, we observed a higher male predominance, present in a proportion of 60%. This result is supported by studies in the literature confirming a higher incidence of VTE among males [10]. Also, the average age at admission for patients with digestive cancer and VTE was 66 years. The majority of patients were in the age group 60-69 years, four times more than those aged 31-49 years and twice more than those aged 50-59 years. Data from our study are consistent with

the literature, which reports an average age of VTE patients of approximately 65 years [10].

This retrospective study highlights that among digestive cancers, pancreatic cancer is associated with the highest risk of VTE. The number of patients who associated pancreatic cancer and VTE was 58 (28% of the study group). The mechanisms explaining the increased risk of thromboembolic complications in cancer patients are complex and involve several factors. Tumor cells activate hemostasis through various pathways, leading to systemic hypercoagulability. With its procoagulant status, cancer is a major, independent risk factor for VTE [11]. In addition, thromboembolic complications have been shown to be more frequent in patients with digestive cancers [11]. According to literature studies, pancreatic cancer is considered one of the malignant neoplasms with the highest thrombotic risk [11]. Colorectal cancer is the second most common neoplasm in our study group, being present in 53 patients (26.5%). Thromboembolic events are a common cause of mortality in patients with this type of cancer.

The most frequent thromboembolic complications were portal vein thrombosis, DVT and PTE. Portal vein thrombosis was present in the highest number of patients (72 patients), DVT ranked second in frequency (51 patients) and PTE third (34 patients).

Of the digestive neoplasms, the highest rate of complications with VTE was hepatocarcinoma, 65.95%. These findings are consistent with literature data, which indicate portal venous thrombosis as a common complication of liver cancer [12]. Studies have reported the association of portal thrombosis in approximately 25-50% of hepatocarcinoma cases. Direct invasion of the venous wall by cancer cells is one of the main mechanisms of portal vein thrombosis in liver cancer patients.

DVT and PTE were most common in patients with colorectal cancer, and pancreatic cancer ranked second in frequency. According to literature data, pancreatic cancer has the highest risk of thrombotic events among digestive malignancies. However, due to the significantly higher prevalence of colorectal cancer, most cases of VTE are associated with this neoplasm [13].

Our study also followed the frequency of comorbidities among patients with digestive cancers and thromboembolic complications. Of these, hypertension was the most common, occurring in 80 patients (40%). Various studies have investigated the association between blood pressure and VTE risk, and some have reported a greater than 50% risk of developing thrombotic complications in patients with hypertension [11]. However, the results are conflicting, with some studies also stating that the association of this risk factor with thrombotic complications is imprecise [10]. The mechanism of VTE in hypertension is a reduction in oxygenated blood flow, which predisposes the vascular endothelium to hypoxia. The endothelial cell response is inflammation and expression of adhesion molecules, which will activate the coagulation cascade [10].

Diabetes mellitus was diagnosed in 47 patients (23.5%) in the study group. About 96% of these patients had type 2 diabetes mellitus and 4% had type 1 diabetes mellitus. Diabetes mellitus is a chronic disease associated with numerous microvascular and macrovascular complications [14]. The patients with type 2 diabetes mellitus have an extremely high risk of developing cardiovascular diseases, VTE being included among them [14]. Data in the literature indicate that the link between diabetes mellitus and the development of VTE is not fully understood, the main reason being the prothrombotic effect of hyperglycemia [14]. Studies have demonstrated elevated levels of factors II, VII, VIII, fibrinogen and tissue factor in combination with decreased partially activated tromoplastin time and prothrombin time. Suppression of endogenous fibrinolysis and low antithrombin levels in hyperglycemic states are included in the explanation of the procoagulant status in diabetes mellitus [14]. Some studies suggest that the presence of other risk factors, such as obesity, metabolic syndrome or cardiovascular comorbidities in addition to diabetes mellitus make it difficult to directly associate diabetes with venous thrombosis [14].

Regarding immobilization as a risk factor for VTE, in our study it was identified in 32 patients

(16%), with DVT being the most common. According to literature data, lower limb immobilization is a common risk factor for thrombotic complications [15]. Studies also indicate that immobilization is one of the main causes of DVT. Reduced blood flow with the occurrence of venous stasis contributes to the pathophysiology of thrombosis from prolonged immobilization. A period longer than 14 days is associated in studies with a five-fold increased risk of developing DVT [15].

In our study, smoking was present in only 25 patients (12.5%). This is a type of behavior associated with an increased risk for VTE, a dose-dependent risk according to some studies [16]. Smokers may also associate other risk factors, so the likelihood of developing thrombotic complications cannot be explained by smoking alone. Body mass index may influence estimates in the literature on the link between smoking and thrombosis. Even if the risk of VTE associated with smoking is lower than that associated with other factors, smoking is more prevalent (there are 1.1 billion smokers globally) and may act synergistically with other risk factors [16]. Therefore, smoking should be considered when assessing patients for thromboembolic complications.

35% (70 patients) of the patients included in our study had a history of cancer surgery. These results are consistent with data in the literature, in which thromboembolism is described as the leading cause of mortality in oncologic surgical patients [17]. Both cancer and cancer surgery are independent risk factors for VTE. Postoperative immobilization associated with endothelial damage and hypercoagulability, increased complexity of surgical procedures and exposure to neoadjuvant therapies are possible explanations for the increased risk of thromboembolic phenomena [17].

Chemotherapy is a significant risk factor in our analysis, being reported in 64 patients (32% of the total). The chemotherapeutic agents used include Bevacizumab, Capecitabine, Olaparib, Sorafenib, Oxaliplatin and Cisplatin. Of patients treated with a single chemotherapeutic agent, Sorafenib was the most common. Polychemotherapeutic combinations were present in 11% of cases. The most common chemotherapeutic agent combinations were Gemcitabine and Cisplatin, and Gemcitabine and Oxaliplatin, respectively, each occurring in two patients in the study group. Chemotherapy is known in the literature as an important risk factor in the development of VTE. The cytotoxic effect of chemotherapeutic agents on endothelial function may lead to pathophysiologic consequences such as vasoconstriction, stimulation of platelet aggregation and increased procoagulant activity. These mechanisms are cited in the literature as being involved in the pathogenesis of VTE [18]. The combination of the chemotherapeutic Gemcitabine with Cisplatin increases the risk of developing VTE according to specialized studies [18].

In terms of histopathologic diagnosis, in our study we identified only one cancer, adenocarcinoma, the most frequent localization being pancreatic. Not only is chemotherapy associated with an increased risk of VTE, but cancer type also influences the occurrence of thromboembolic complications. Thus, data from the literature confirm our results, with patients with pancreatic adenocarcinoma being at increased risk of developing venous thrombosis [19]. Regarding the degree of differentiation and tumor stage, this information was only available in a limited number of patients. We observed, however, that most patients had poorly differentiated tumors (18 patients grade 3 and two patients grade 4) and advanced tumor stages (24 patients stage 4, two patients stage 3C, and one patient stage 3B). According to the literature, patients with advanced stages of cancer are at increased risk of developing thromboembolic phenomena. Also, the degree of tumor differentiation has been shown to be a valuable histopathologic parameter for thrombotic risk stratification. Thus, patients with poorly differentiated tumors (G3 or G4) have a higher thrombotic risk compared to patients with well-differentiated tumors (G1 or G2) [19].

Infectious complications were observed in 26.5% of patients. In this context, sepsis was most common, affecting 10% of all patients included in the study. Other notable infections in this analysis were bronchopneumonia and *Clostridioides difficile* enterocolitis. In the

literature, infections are known as predisposing factors for VTE. Sepsis is a significant risk factor for VTE. The pathogenesis of this correlation is not fully elucidated, but may be the result of several factors including immobilization, activation of thrombo-inflammatory signaling pathways, disseminated intravascular coagulation and venous stasis [20]. Epidemiologic studies have shown that the risk of venous thrombosis is also increased in respiratory tract infections. Hypotheses about the mechanisms involved have included activation of the coagulation cascade and inhibition of anticoagulant factors. This has been observed in both sepsis and pneumonia. Studies have shown that bacterial wall lipopolysaccharide may mediate platelet activation, favoring the occurrence of thrombotic complications [21]. The proinflammatory status in pneumonia stimulates tissue factor secretion by alveolar macrophages and alveolar epithelial cells [21]. In the literature, there is the hypothesis that tissue factor is a key mechanism in the activation of the coagulation cascade in infections. The risk of VTE in *Clostridioides difficile* enterocolitis is explained by studies through the activation of inflammasomes. This phenomenon is related to the relationship between inflammatory and thrombotic processes. Inflammatory mechanisms alter the balance between prothrombotic and antithrombotic factors, thus favoring thrombus formation. The influence of inflammasomes in the pathophysiology of inflammatory diseases with a prothrombotic phenotype confirms the interaction between thrombosis and inflammation.

The in-hospital death rate was 23.5%, and the 5-year death rate was 82.5%. The results are consistent with the literature, VTE being associated with a significant mortality rate in both the general population and cancer patients.

Author contributions:

Conceptualization, V.A.I., A.E.B., G.G., V.B., and C.L.T..; methodology, V.A.I.; software, V.A.I.; validation, C.C.D..; formal analysis, G.G.; investigation, A.E.B., V.B; resources, C.C.D.; data curation, V.A.I. and G.G.; writing—original draft preparation, V.A.I., G.G.; writing—review and editing, G.G.; visualization, C.C.D.; supervision, G.G.; project administration, C.C.D. All the authors have read and agreed with the final version of the article

Compliance with Ethics Requirements:

"The authors declare no conflict of interest regarding this article".

"The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national law. Informed consent was obtained from all the patients included in the study"

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