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Assessment of coagulation profile in patients with breast cancer in Saudi Arabia

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ABSTRACT

Background: The most common malignancy in women is breast cancer. It is associated with significant morbidity and mortality. One of the under estimated complications with breast cancer is the abnormalities occurring in the coagulation profile of patients. *Objective:* The aim of the study is to assess the coagulation profile of patients with breast cancer in Saudi Arabia. *Design and Setting:* This is a retrospective study conducted in kingdom of Saudi Arabia, which involved collecting data from patients' records. Included demographic information of patients, and information on their type of cancer and the results of laboratory investigations. Data analysis was executed through Graph pad prism and SPSS. *Results:* Data was collected from records of 105 patients. 88.6% were females; mean age 56.9± 14.5 years old, 60% were in the age group between 41 to 60. 95.2% of patients had cancer, where 31.4% of the patients had breast cancer, and 41% had invasive duct carcinoma, while 3.8% had infiltrating duct carcinoma. 18.1% had high random blood glucose, while 3.8% had high PTT values, and 16.2% had high PT levels, while 2.9% had high INR levels. Random blood glucose (p-value=0.03), PTT (p-value=0.043), PT (p-value<0.001) and INR (p-value<0.001) were significantly higher in breast cancer patients. Also, lower proportion of breast cancer patients had normal random blood glucose (p-value=0.009), PT (p-value=0.029) and INR (p-value=0.025). *Conclusion:* Breast cancer patients are more common to have coagulation abnormalities in terms of elevated bleeding risk. Future studies should examine the other coagulation factors in such patient population.

Keywords: Coagulation, breast cancer.

1. INTRODUCTION

In 2010, Breast cancer was ranked as the ninth leading cause of death among Saudi females (Bowser et al., 2017). Moreover, about one fourth of all cancer patients registered in Saudi women had breast cancer (Youlden et al., 2012). It is also proposed that the incidence will grow with in the upcoming years due to the increasing breast cancer population and prolonged survival (Shulman et al., 2010). Recently, there is a growing interest in the correlation between coagulation abnormalities and different types of cancer (Roy et al., 2017). One

of the well established risk factors for thrombosis is cancer. The incidence of thromboembolism among cancer patients is four to ten folds higher than those estimated in the general population (Mandoj et al., 2018). The risk is notably higher in patients with brain or pancreatic cancer. Consequently, venous thromboembolism prophylaxis is becoming a part of the treatment strategy for some cancer patients (Mi et al., 2017). Furthermore, some coagulation bio markers are used for the prognosis of some types of cancer, including lung, ovarian, and colorectal cancer, regardless of the diagnosis of thrombosis (Yuan et al., 2017). Concerning breast cancer, there is increasing evidence that coagulation can be associated with significant complications in both the early and advanced stages of the disease (Lee et al., 2017). Some studies reported a positive association between D dimer levels and breast cancer prognosis in relation to angiogenesis. Furthermore, it has been correlated to circulating tumor cells in patients with metastatic disease, which was also linked to venous thromboembolism diagnosis (Kirwan et al., 2020).

Additionally, coagulation factors have been linked to the genotypes and phenotype status in breast cancer patients (Levi, 2016). Some of these factors (particularly D Dimer) were correlated to the type of hormone receptor status (Swier and Versteeg, 2017). Furthermore, the coagulation inhibitors protein C and Ant thrombin were reduced in the plasma of these patients, while there was an increase in tissue factor pathway inhibitor during the progression of the cancer. For instant, an association has been established between common SNPs in genes of the tissue factor pathway inhibitor pathway including gene *F5, F10,* and *EPCR* and breast cancer susceptibility and progression. Despite the information available on the diagnosis as well as thromboembolic incidents therapy in cancer patients (Wojtukiewicz et al., 2016). Data are scarce on the correlation between common coagulation factors that are routinely measured in cancer patients (i.e., International normalized ratio, pro thrombin time, and activated pro thrombin time). Previous studies among cancer patients at different occasions in Taif city has found several interesting findings such as prevalence of anaemia (Almehmadi et al., 2021), vitamin D deficiencies(Almehmadi et al., 2020b), hypoproteinaemia (Mazen Almehmadi, 2020), leukocytosis (MM Almehmadi, 2020), and dysregulation of electrolytes (Abdulaziz and Almehmadi, 2021), and irregulated levels of thyroid hormones(Almehmadi et al., 2020a). Accordingly, the purpose of the present study is to look at the connection between breast cancer and coagulation using a routine coagulation profile and comparing it to patients who had other types of cancer in Saudi Arabia.

2. MATERIALS AND METHODS

Study design

This retrospective study was performed in Saudi Arabia; involving data collection from patients' records lasted from September 2021 until March 2022. All adult females were who cancer had been eligible for inclusion.

Data collection

A pre designed excel sheet was used for data collection. Demographic information of the patients was collected, along with information about their cancer, including its site and type. Laboratory information was also collected, including fasting blood glucose, INR, PT, and PTT levels.

Statistical analyses

For categorical variables, data were described using frequencies and percentages, whereas means and standard deviations were used to explain numerical variables. One way ANOVA analysis was used to compare means among different groups, while chi square testing was used to compare categorical variables. All P values < 0.05 were considered statistically significant. IBM SPSS (Statistical Package for the Social Science; All statistical computations were carried out using IBM Corp's version 26 for Microsoft Windows (Armonk, NY, USA).

Ethical considerations

Ethics board approval was acquired before conducting any study procedure (IRB: HAP-02-T-067). Confidentiality of the identity of patients was kept during the study.

3. RESULTS

One hundred and five patients were eligible for inclusion. The demographics of patients and the analysis of the collected data are shown below.

General Characters of responders

Out of 105 patients, 88.6% were females, while 11.4% were males. As for age, six age groups were assigned to it. Starting from 20 and ending with 70 years old. 29.5% were in the age group between 41 to 50, and a similar percentage was between 51 to 60; the mean age was 56.9± 14.5 years old, as shown in table 1.

Table 1 shows patients' demographics.

	group	Count	Percent
Gender	Male	12	11.4
	Female	93	88.6
Age group	20 to 30	2	1.9
	31 to 40	8	7.6
	41 to 50	31	29.5
	51 to 60	31	29.5
	61 to 70	12	11.4
	More than 70	21	20.0

Cancer diagnosis

The diagnosis of cancer was also reported. 31.4% of the patients had breast cancer, and 95.2% had any type of cancer. The most prevalent type of cancer was left breast cancer, in 18% of the cancer patients, followed by 15% with right breast cancer, while the least prevalent type was uterine carcinoma, in only 1% of patients with cancer. Furthermore, 41% of patients had invasive duct carcinoma, while 3.8% had to infiltrate duct carcinoma (NOS), as shown in table 2 and figure 1.

Table 2 Cancer diagnosis

	Type of cancer	Count	Percent
Diagnosis	Breast cancer	33	31.4
	Non-breast cancer	72	68.6
Cancer lesions	Cancer	100	95.2
	Non-cancer	5	4.8
Type of cancer	Left breast cancer	18	18
	Right breast cancer	15	15
	Endometrial Adenocarcinoma	9	9
	Endometrial carcinoma	5	5
	Cervical cancer	4	4
	Uterine carcinoma	1	1
	Other types	48	48
Type of cancer	Invasive Duct Carcinoma	43	41.0
	Adenocarcinoma	18	17.1
	Endometrioid adenocarcinoma	11	10.5
	Invasive Lobular Carcinoma	4	3.8
	Infiltrating Duct Carcinoma (NOS)	4	3.8
	Other types	25	23.8

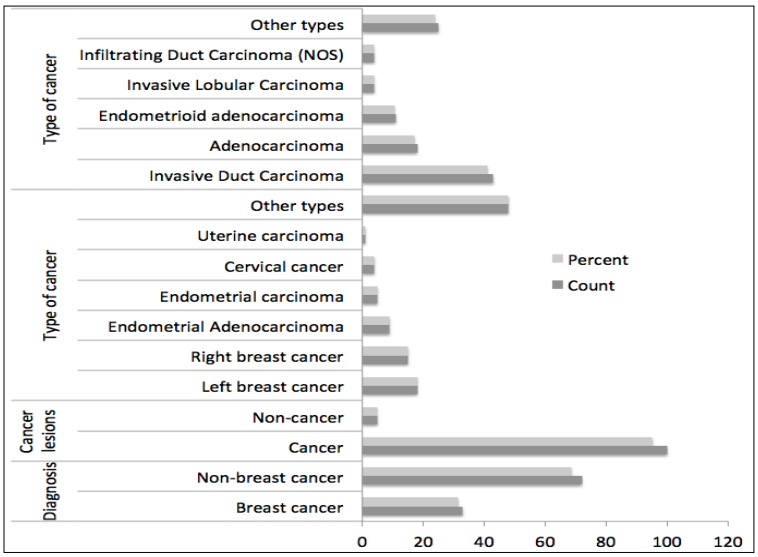

Figure 1 cancer diagnosis of patients.

Laboratory results

Laboratory values for random blood glucose, pro thrombin time (PTT), thrombin time (PT), and international normalized ratio for every patient were reported. The mean random blood glucose was 129.7±85.9 mg/dl, mean PPT was 31.4±6.8, while mean PT was 13.1±11.9 and mean INR was 0.96±0.16, as shown in table 3 and figure 2.

Table 3 Laboratory results

Test	Count	Missing	Mean	SD	Min	Max
Random blood glucose	105	0	129.7	85.9	49.8	614.4
PTT	105	0	31.4	6.8	20.08	83.0
PT	105	0	13.1	11.9	8.0	20.0
INR	105	0	0.96	0.16	0.6	1.5

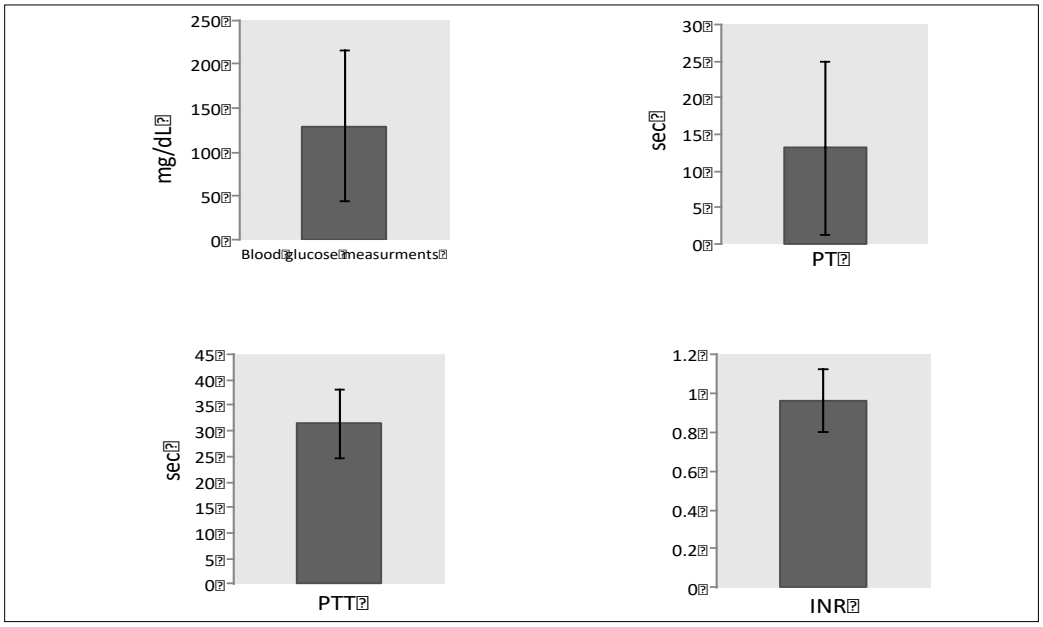

Figure 2 Laboratory results for a) random blood glucose, b) pro thrombin time (PTT), c) thrombin time (PT), and d) international normalized ratio for all participants.

Furthermore, 18.1% had high random blood glucose, while 3.8% had high PTT values, and 16.2% had high PT levels, while 2.9% had high INR levels, as shown in table 4 and figure 3.

Table 4 Categorization of laboratory results.

Test	Level	Count	Percent
Random blood glucose	Low	5	4.8
	Normal	81	77.1
	High	19	18.1
PTT	Low	14	13.3
	Normal	87	82.9
	High	4	3.8
PT	Low	13	12.4
	Normal	75	71.4
	High	17	16.2
INR	Low	95	90.5
	Normal	7	6.7
	High	3	2.9

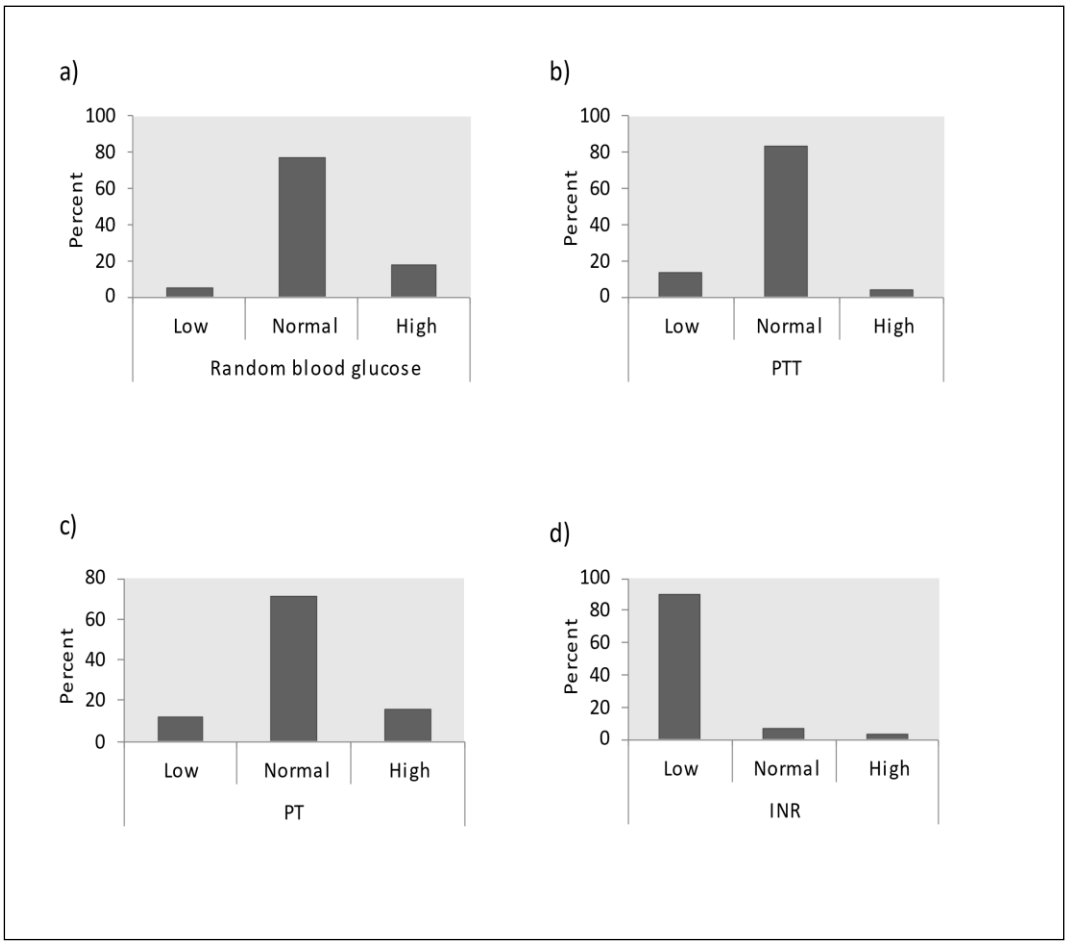

Figure 3 shows a) 18.1% had high random blood glucose, while b) 3.8% had high PTT values, and c) 16.2% had high PT levels, while d) 2.9% had high INR levels

Comparison of laboratory data over patients with and without breast cancer

One way ANOVA testing was used to compare patients with breast and non-breast cancer at a level of significance p-value<0.05. It has been shown that random blood glucose (p-value=0.03), PTT (p-value=0.043), PT (p-value<0.001) and INR (p-value<0.001) were significantly higher in breast cancer patients, as shown in table 5 and figure 4.

Table 5 Comparison between breast and non-breast cancer using one way ANOVA

Test		Diagnosis	Count	Mean	SD	Minimum	Maximum	P-value
Random blood glucose	Type of cancer	Breast Cancer	33	103.0	38.5	49.8	266.0	0.030
		Non-Breast Cancer	72	142.0	98.3	64.1	614.4	
PTT	Type of cancer	Breast Cancer	33	33.4	9.9	24.2	83.0	0.043
		Non-Breast Cancer	72	30.5	4.7	20.1	40.5	
PT	Type of cancer	Breast Cancer	33	14.2	1.4	12.6	18.4	<0.001
		Non-Breast Cancer	72	12.6	2.0	8.0	20.0	
INR	Type of cancer	Breast Cancer	33	1.1	0.1	0.9	1.5	<0.001
		Non-Breast Cancer	72	0.9	0.2	0.6	1.3	

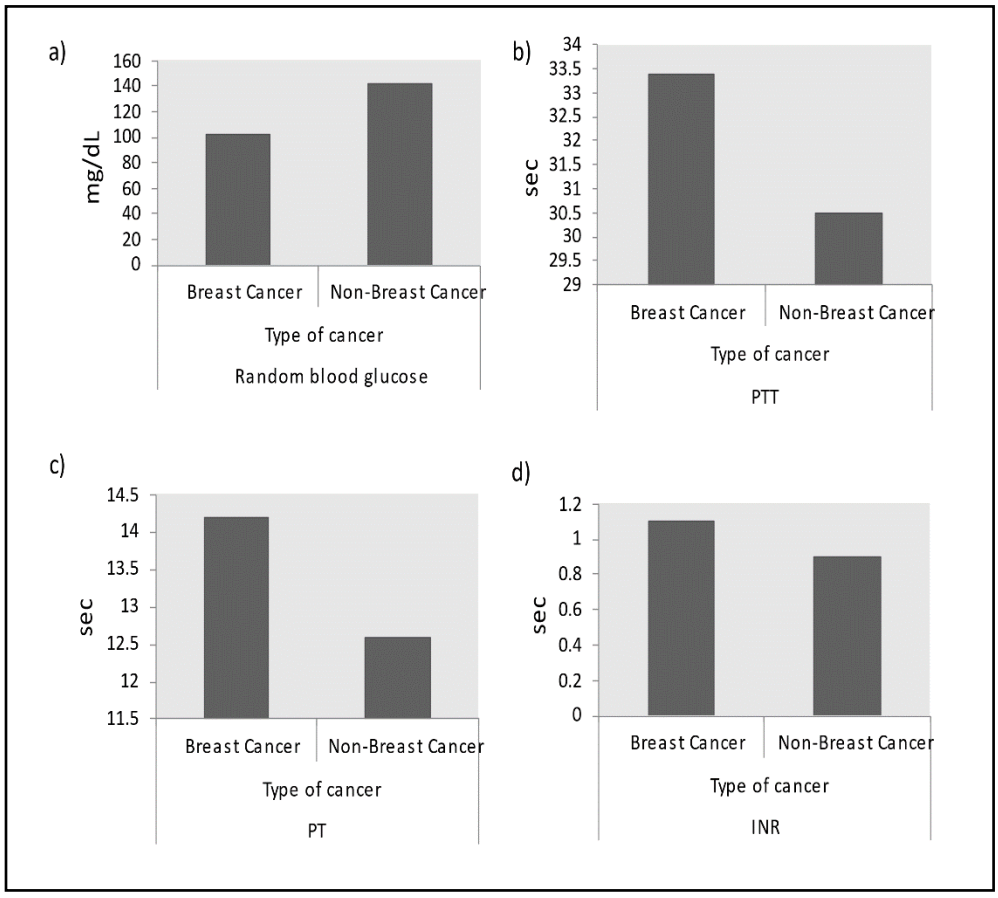

Figure 4 One way ANOVA testing was used to compare patients with breast and non-breast cancer at a level of significance, that a) random blood glucose, b) PTT, c) PT and d) INR.

Furthermore, using chi square testing, a significantly lower proportion of breast cancer patients had normal random blood glucose (p-value=0.009), PT (p-value=0.029), and INR (p-value=0.025), as shown in table 6 and figure 5.

Table 6 Comparison between breast and non-breast cancer using chi square testing

Test	Level	Breast Cancer	Non-breast cancer	P-value
Random blood glucose	Low	80.0%	20.0%	0.009
	Normal	33.3%	66.7%	
	High	10.5%	89.5%	
PTT	Low	14.3%	85.7%	0.065
	Normal	32.2%	67.8%	
	High	75.0%	25.0%	
PT	Low	0.0%	100.0%	0.029
	Normal	34.7%	65.3%	
	High	41.2%	58.8%	
INR	Low	28.4%	71.6%	0.025
	Normal	42.9%	57.1%	
	High	100.0%	0.0%	

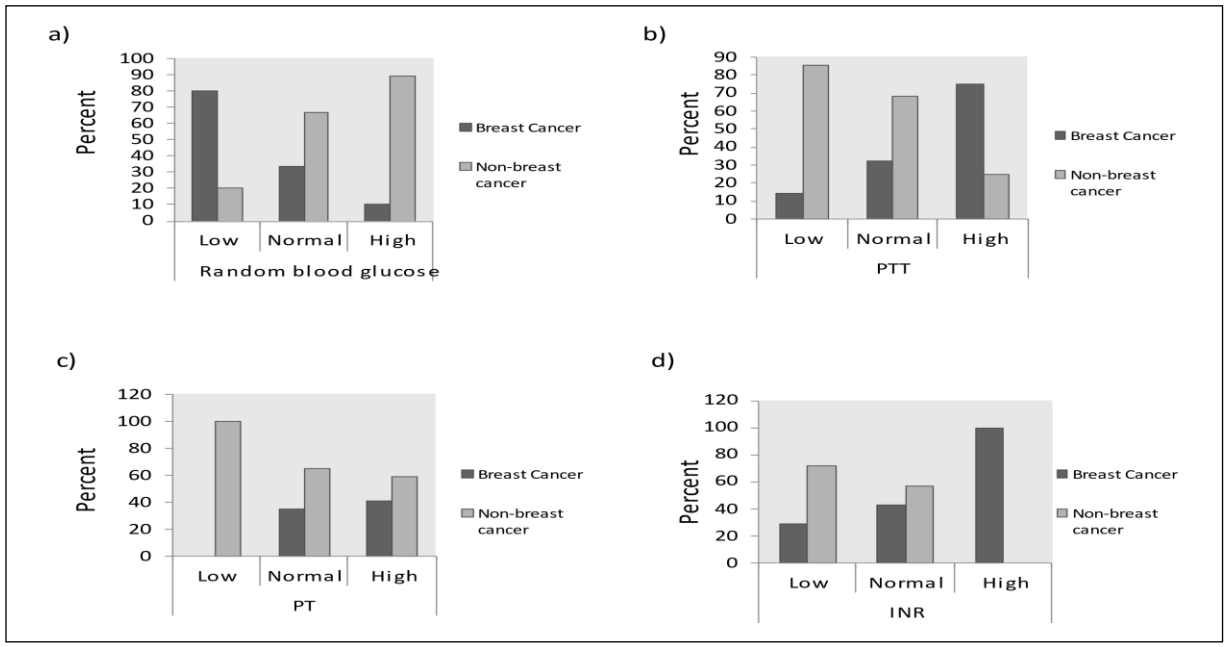

Figure 5 chi square testing, a significantly lower proportion of breast cancer patients had normal random blood glucose (p-value=0.009), PT (p-value=0.029), and INR.

4. DISCUSSION

Cancer is a multi system disease that usually has systemic implications. Patients with cancer suffer from increased bleeding risk, as well as an increased coagulation risk (Sasaki et al., 2018). These risks may put the life of patients in danger. Despite the data available on cancer patients' coagulation, the data on breast cancer patients is scarce (Nagy, 2013). Understanding coagulation in this population can guide better treatment strategies and lower complications (Tinholt et al., 2018). The present study examined the coagulation abnormalities in breast cancer patients in Saudi Arabia. The study included patients with and without breast cancer and compared them. 31.4% of the whole cohort had breast cancer. The study demonstrated that patients with breast cancer were at higher risk of bleeding than other types of cancer. This higher risk was demonstrated by a significantly higher random blood glucose (p-value=0.03), PTT (p-value=0.043), PT (p-value<0.001) and INR (p-value<0.001) in the breast cancer patients. Furthermore, 18.1% had high random blood glucose, while 3.8% had high PTT values, and 16.2% had high PT levels, while 2.9% had high INR levels.

Coagulation in breast cancer patients has been assessed in different settings. Lal et al., (2013) reviewed the changes in platelets and coagulation factors in patients with advanced breast cancer. Lal et al., (2013) demonstrated that hemostatic changes could be a

predictor for cancer progression. Additionally, these changes can be novel treatment targets for advanced cancer. There was a significant correlation between breast cancer and abnormal coagulation profile in the present study, which demonstrated an increased risk of bleeding. Patients with breast cancer showed more abnormalities in coagulation profile compared to other types of cancer. Also, most of the abnormalities appeared in the PT levels, where 16.2% of the patients showed abnormalities (Mego et al., 2015). Latest research examined the relationship between breast cancer and the risk of venous thrombo embolism in patients with metastasis. By including 116 patients in a prospective study Mego et al., (2015) showed that the circulating tumor cells were significantly correlated to increased coagulation and thrombosis risk.

In the present study, the risk of coagulation could not be evaluated. However, the coagulation profile abnormalities demonstrated an increased risk of bleeding in breast cancer patients through the evaluation of INR, PTT, and PT. Moreover, random blood glucose was also evaluated. It was significantly higher in breast cancer patients. Random blood glucose was not evaluated by (Mego et al., 2015). Also, Tas et al., (2014) examined the association between coagulation tests and pathological factors in breast cancer patients included 123 breast cancer patients, while one fifth of the patients had metastatic disease. There were significantly higher levels of D Dimer levels in patients with breast cancer. Additionally, they showed that patients with a more advanced breast cancer stage had significantly higher INR levels (Tas et al., 2014). The findings from Tas research are consistent with the findings from the present study. Breast cancer patients showed higher levels of bleeding markers. As for the type of cancer, 41% of the patients had invasive duct carcinoma. This type of cancer can demonstrate that patients with advanced breast cancer disease are related to bleeding risk (Tas et al., 2014).

However, the present study had some limitations; the study's retrospective nature may have led to the risk of missing or incorrect information for some laboratory values for patients. Additionally, this study was conducted in a single center setting, which causes a limitation on external validity. These limitations should be taken into consideration in any future studies.

5. CONCLUSION

A substantial increase in the chance of coagulation disorders was seen in patients with breast cancer, especially the risk of bleeding. Random blood sugar also showed some abnormalities that should be investigated in future studies. These findings should be considered by clinicians and surgeons dealing with breast cancer, significantly before interventions to minimize bleeding risk. Also, this risk should be evaluated thoroughly for each patient when considering venous thromboembolism prophylaxis. Similar more extensive studies with a prospective design should be encouraged.

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Ethical approval

The study was approved by the Medical Ethics Committee (IRB: HAP-02-T-067).

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Conflict of interest

The authors declare that there is no conflict of interests

Data and materials availability

All data associated with this study are present in the paper.

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