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Coagulation profiles of breast cancer patients attending at cancer treatment centres in Northwest Ethiopia 2023: a comparative cross-sectional study

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Breast cancer is the primary cause of cancer-related deaths in women, especially in developing nations where early detection and comorbidity management are challenging. Coagulopathy significantly enhance the disease severity, but its impact on Ethiopian patients is unclear. Therefore, this study aims to investigate and compare coagulation profiles in chemotherapy-experienced, chemotherapy-naive breast cancer patients, and healthy controls. An Institutional-based comparative cross-sectional study was conducted at the University of Gondar and Felege Hiwot Comprehensive Specialized Hospitals from 15 May 2023 to 30 August 2023 on a total of 180 participants. Participants socio-demographic and clinical data were collected using structured questionnaires in face-to-face interviews and medical record reviews. Blood sample for laboratory tests were taken, with 3 ml in ethylenediaminetetraacetic acid, 3 ml in trisodium citrate, and 2 ml in serum separator tubes. Coagulation parameters were measured using *Genrui coagulation analyser (CA51)* and *Sysmex KX-21 hematology analyser*. Data entry was done using Epi Data version 4.6 and transform to SPSS version 25 for analysis then descriptive statistics was presenting with tables. One-way ANOVA and Kruskal–Wallis tests were used to compare coagulation parameters among the three study groups, considering normal and skewed data, respectively. The activated partial thromboplastin time in chemotherapy-experienced, chemotherapy-naïve patients, and healthy controls showed median ± IQR values of 34.3 ± 15.8, 35 ± 13.3, and 29.2 ± 5.9 s, respectively, indicating a significant difference (p: 0.016). Similarly, the prothrombin time in the same groups had median ± IQR values of 15 ± 3.9, 15.3 ± 2.9, and 13.2 ± 1.9 s, respectively, with a significant difference (p < 0.001). Platelet count mean ± SD in chemotherapy-experienced, chemotherapy-naïve patients, and healthy controls were 351.3 ± 99.6, 345.6 ± 117.5, and 284.3 ± 79.3, respectively, showing a significant difference (*p* < 0.001). The mean ± SD of mean platelet volume in the same groups were 10.4 ± 2.7, 9.5 ± 2.4, and 9 ± 1.2, respectively, with a significant difference (*p*: 0.003). Coagulation parameters of both chemotherapy-experienced and chemotherapy-naïve patients were abnormally prolonged compared to healthy controls. This event indicates in vivo coagulation and it may increase bleeding tendency in patients. Therefore, early laboratory investigation of the coagulation profiles of breast cancer patients is critical for early detection and intervention of the coagulopathy.

Keywords Breast cancer, Coagulation profile, Platelet parameters, Ethiopia

Abbreviations

aPTT	Activated partial thromboplastin time
DIC	Disseminated intravascular coagulation
FHCSH	Felege Hiwot comprehensive specialized hospital
HCG	Human chorionic gonadotropin
HIV	Human immunodeficiency virus

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MPV	Mean platelet volume
PDW	Platelet distribution width
PT	Prothrombin time
TE	Thromboembolism
TF	Tissue factor
UoG-CSH	University of Gondar Comprehensive and Specialized Hospital

Breast cancer, marked by abnormal cell growth, which driven by DNA mutations, can start in one or both breasts and metastasize to distant organs through blood and lymphatic pathways[1]. It is the most prevalent type of cancer, representing 1 in 8 cancer diagnoses and accounting for 2.3 million new cases and 685,000 deaths globally in 2020[2]. According to 2022 report from World Health Organization, it is estimated that by 2040, there will be over 3 million new cases and more than 1 million deaths from breast cancer annually[3]. The disease is more prevalent in nations undergoing economic transformation, such as Ethiopia, where it is frequently diagnosed among women[4]. In 2020, Ethiopia had 16,133 new cases of breast cancer, accounting for 20.9% of all cancer diagnoses in the country[5].

Chemotherapy is commonly employed treatment for breast cancer[6,7], involving the use of anti-cancer drugs to eliminate cancer cells[8]. In Ethiopia, it is the most frequently utilized treatment, administered through the bloodstream, which may potentially impact the balance of the haemostasis[9]. Haemostasis is a tightly regulated physiological system that prevents excessive bleeding by maintaining a delicate balance between procoagulant and anticoagulant processes[10,11]. Cancer cells and chemotherapy drugs in breast cancer treatment disrupt this balanced process and leading to thrombotic events such as Disseminated Intravascular Coagulation (DIC) and Thromboembolism (TE), accompanied by an increased tendency for bleeding[12,13]. These complications compromise the survival prospects of patients[14].

Cancer cells instigates a state of hypercoagulation[15] by modifying both plasma and cellular components of haemostasis either through direct synthesis and secretion of procoagulants or indirectly via intracellular cytokine-mediated mechanisms[16]. Moreover, chemotherapy drugs also exacerbate hypercoagulation[17] through reducing the concentrations of coagulation inhibitors, like protein C and protein S[18] and increase the releasing of procoagulants and proinflammatory cytokines from damaged cancer cells[19,20]. The direct toxicity of the drug on the vascular endothelium also contributes to other mechanisms of hypercoagulation in patients undergoing chemotherapy[19,20].

Cancer cells also induce platelet activations that involve shape changes, release of small molecules and proteins, and membrane-based alterations[21,22]. The main mechanism of platelet activation is cancer cell-induced platelet aggregation, either through direct contact with tumor cells or via mediators like adenosine diphosphate, thromboxane A2, or serine proteinases such as thrombin[23]. In addition, the generation of matrix metalloproteinase by cancer cells and the general activation of the coagulation system are other ways of platelet activation[24].

Clinically significant haemostatic abnormalities, including thrombosis and haemorrhage, impact up to 15% of cancer patients, representing the second most common cause of mortality in breast cancer patients[25]. Moreover, 10% of advanced disease patients have at least one bleeding episode[26]. In comparison to estimates for the general population, the incidence of TE in breast cancer patients is 4 to 10 times higher[14]. Furthermore, patients undergoing chemotherapy face an increased risk of coagulopathy[27], which has a negative impacts on the disease-free and overall survival of patients[6]. Venous TE is a common side effect of chemotherapy drugs, affecting 5–10% of early-stage and 17% of advanced breast cancer patients[18].

Therefore, this study aims to address an important gap in understanding the coagulation disorder of breast cancer patients, particularly in the context of chemotherapy, in resource-limited settings like Ethiopia. Assessing coagulation profiles among chemotherapy-experienced and chemotherapy-naïve patients compared to healthy controls can provide valuable insights into how cancer and its treatment impact the coagulation system.

Methods and materials

Study design

A comparative, institution-based cross-sectional study was conducted from May 15, 2023, to August 30, 2023, at the University of Gondar Comprehensive and Specialized Hospital (UoG-CSH) and Felege Hiwot Comprehensive Specialized Hospital (FHCSH) in Northwest Ethiopia.

Study area

The study was conducted at UoG-CSH and FHCSH in Northwest Ethiopia. UoG-CSH is a teaching hospital located in Gondar, approximately 750 km from Addis Ababa. It serves over 7 million people and features a large oncology unit with 32 beds, treating more than 3,000 cancer patients annually[28]. On the other hand, FHCSH is found in Bahr Dar town the capital of Amhara regional state and 565 km away from Addis Ababa. It serves more than 7 million people and contain an oncology unit equipped with 18 beds[29]. Both oncology units have oncologists, trained nurses, and pharmacists for comprehensive patient care[30].

Population and sampling

The source population for the study participants were all confirmed breast cancer patients and apparently healthy individuals at the UoG-CSH and FHCSH. The study population comprised both chemotherapy-experienced and chemotherapy-naïve patients, as well as apparently healthy individuals attending the oncology units during the study period. Cases and controls were matched based on age and sex. According to the guidelines set by Van Voorhis and Morgan, a minimum of 30 individuals per group is required to detect significant differences between groups, ensuring an 80% power level in a comparative study[31]. Based on this rule 60 breast cancer

patients who had undergone chemotherapy, 60 breast cancer patients who had not yet received chemotherapy, and 60 apparently healthy individuals were enrolled in the study (Fig. 1).

Inclusion and exclusion criteria

The study included breast cancer patients who were chemotherapy-naïve and who had undergone a minimum of 4 cycles of chemotherapy, attended the oncology units of UoG-CSH and FHCSH during the study period, and agreed to participate. Similarly, apparently healthy female individuals who were voluntarily agreed to participate were recruited as healthy controls.

The study excluded breast cancer patients with a history of thrombosis, heparin or warfarin treatment, haematological malignancies, other solid cancers besides breast cancer, infectious diseases (malaria, Schistosoma, hepatitis B or C viruses, HIV), known chronic diseases (liver disease, kidney disease, hypertension, diabetes mellitus), family history of bleeding disorders, pregnancy, and alternative treatments for breast cancer (hormonal, targeted, radiation therapy). In addition, apparently healthy individuals with a family history of bleeding, severe bleeding within 3 months, pregnancy, and positive for malaria, Schistosoma, hepatitis B or C viruses, and HIV were also excluded from the study.

Study variables

Coagulation parameters, such as Activated Partial Thromboplastin Time (aPTT), Prothrombin Time (PT), Platelet count, Mean Platelet Volume (MPV), and Platelet Distribution Width (PDW) are dependent variables for the study. Whereas, socio-demographic characteristics such as age, sex, residence, educational status, marital status, menopause status, and occupations, as well as Clinical characteristics such as anatomical site of cancer, stage of disease, chemotherapy-exposure, drug regimen, and treatment cycle of the study participants were independent variables for the study.

Operational definitions

- *Chemotherapy-experienced* breast cancer patients who had undergone a minimum of 4 cycles of chemotherapy treatment.
- *Chemotherapy-naïve* breast cancer patients who haven't exposed to chemotherapy drug.
- *Abnormally prolonged and short aPTT* defined as a measurement exceeding 36 s and falling below 26 s, respectively[32].
- *Abnormally prolonged and short PT* defined as a measurement exceeding 14 s and falling below 11 s, respectively[32].
- *Thrombocytosis and Thrombocytopenia* considered when blood platelet count $> 399 \times 10^3$ and $< 90 \times 10^3$ cells/μl, respectively[33].
- *Abnormally high and low MPV* considered when MPV > 12.3FL and < 8FL, respectively[33].
- *Apparently healthy control* An individual who is in good physical health relative to their age and physiological status, without detectable diseases or disabilities[34].

Data collection procedure

Socio-demographic and clinical data collection

The socio-demographic data has been collected using a pre-tested structured questionnaire via face-to-face interview. Clinical data pertaining to breast cancer patients were retrieved by reviewing their medical records using a structured data extraction form. The presence of underlying chronic conditions such as kidney disease, liver disease, hypertension, diabetes mellitus, hematological malignancies, and other solid cancers, as well as any on-going treatment with heparin or warfarin, were evaluated through direct interviews and thorough examination of medical records. Additionally, details regarding family history of bleeding disorders were

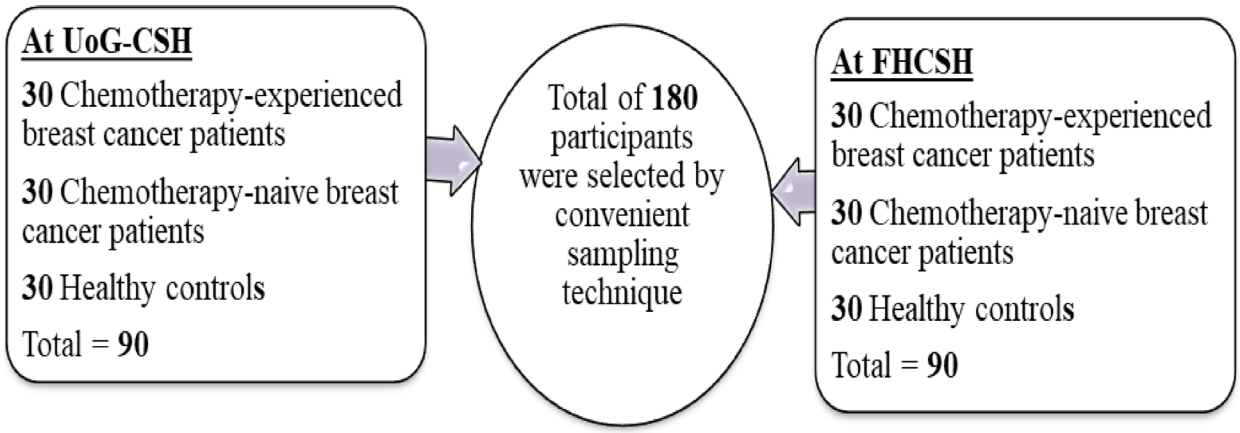


Fig. 1. Study participant recruitment techniques at the UoG-CSH and FHCSH cancer treatment center, Northwest Ethiopia, (N = 180), 2023.

obtained through face-to-face interviews. Participants' statuses regarding hepatitis B and C viruses, HIV, malaria, Schistosoma infections, and pregnancy were determined through laboratory tests performed by skilled laboratory professionals.

Laboratory sample collection and processing

A total of 8 ml venous blood, about 3–5 ml urine and pea size stool samples were collected from each study participant for laboratory analysis (Fig. 2).

After laboratory samples collection, platelet parameter analysis was performed from whole blood, and serum screening for HIV, hepatitis B and C infections was performed. In addition, Human Chorionic Gonadotropin (HCG) tests, microscopic stool examination and microscopic examination of 3% Giemsa-stained blood film were performed for screening of pregnancy, Schistosoma and malaria, respectively. For aPTT and PT samples, centrifugation was performed, and 1–2 ml of plasma was separated and stored with a neck tube in a deep freezer under − 70 °C[35] (Fig. 3).

Laboratory analysis

Platelet parameters, including platelet count, MPV, and PDW were measured using the automated *hematological analyzer, (Sysmex kx-21, Japan)* employing the electric impedance principle[36]. The standard operating procedures, daily maintenance, weekly maintenance, and internal quality control procedures for the analyser were strictly adhered throughout the research process. Coagulation tests, specifically aPTT and PT, were analyzed using the semi-automated *Genrui Coagulation Analyzer* (*CA51, China*)[37]. The *Genrui Coagulation Analyzer* offers a rapid and straightforward measurement of PT and aPTT in seconds, utilizing a coagulometric (turbid metric) clot detection approach[37].

Screening tests for HIV, hepatitis B virus, hepatitis C virus and pregnancy were conducted using the STAT-PAK, HBsAg, HCV antibody and HCG test kits, respectively. Malaria infection in participants was assessed by examining 3% Giemsa-stained blood films. Wet mount and concentration stool examinations were done to detect Schistosoma infection. Stool samples were examined within 2 h, and delayed ones were preserved with 10% formalin for quality. Participants who were negative for all these tests were included in the study.

Quality control for data collection and laboratory analysis

The quality of socio-demographic and clinical data was ensured by initially preparing the questionnaire in English and then translating it into Amharic. A pre-testing phase was conducted on 5% of the planned sample size at the Tibebe Ghion Specialized Hospital oncology unit. Data collectors received thorough orientation before

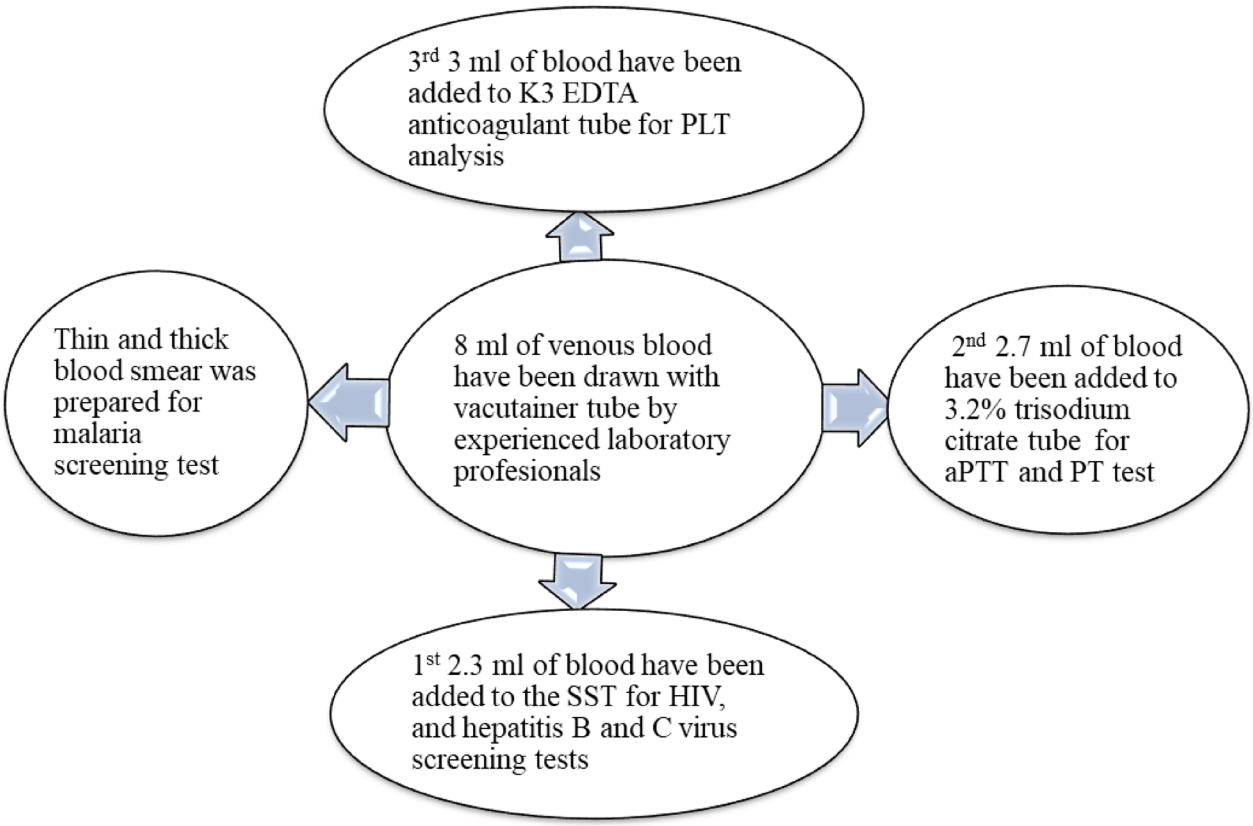


Fig. 2. Blood sample collection process of the study participants at the UoG-CSH and FHCSH cancer treatment center, Northwest Ethiopia, (N = 180), 2023.

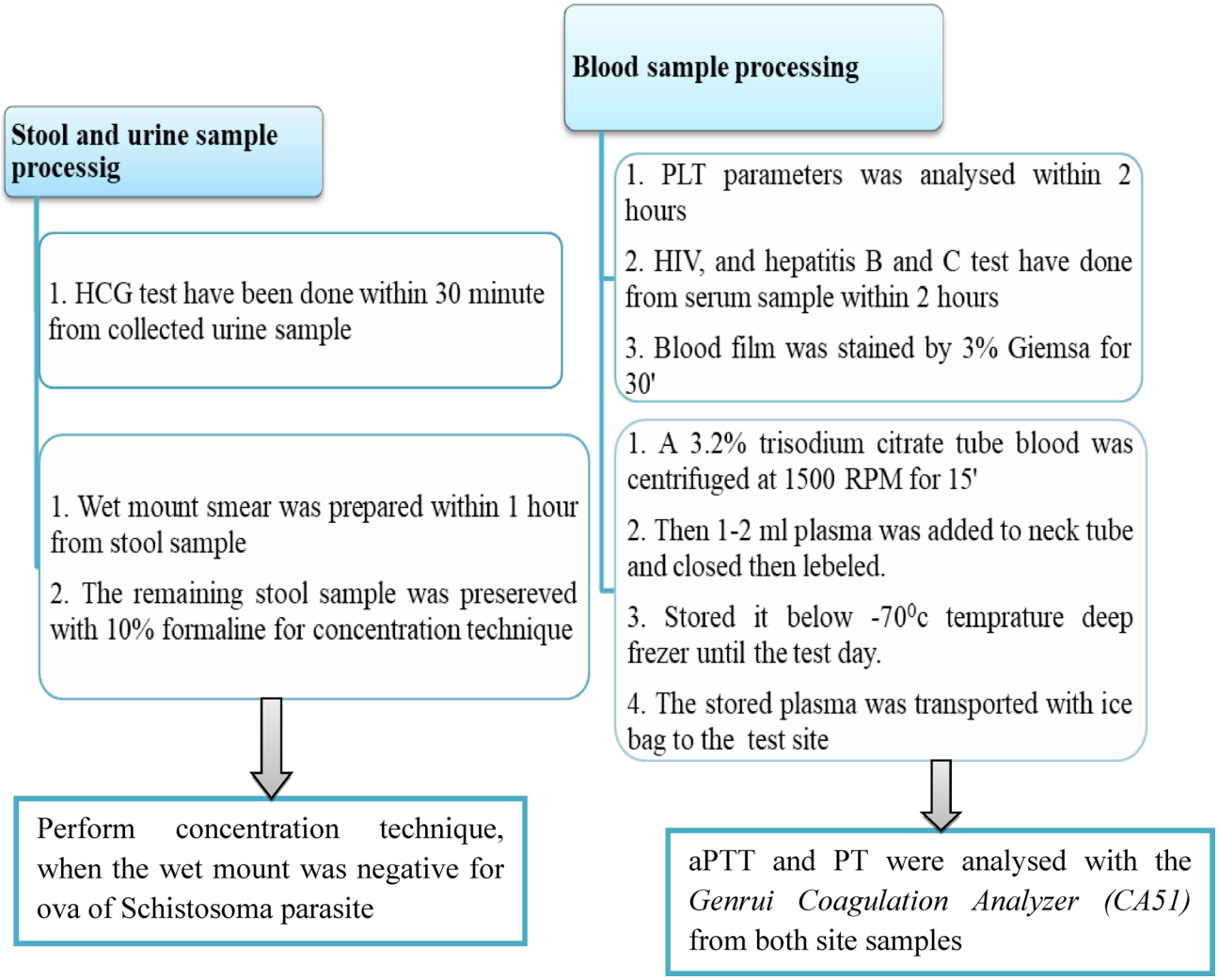


Fig. 3. Laboratory sample processing and storage at the UoG-CSH and FHCSH cancer treatment center, Northwest Ethiopia, 2023.

commencing the actual data collection. Rigorous supervision was maintained throughout the data collection phase to guarantee the accuracy and reliability of the collected information.

During platelet analysis, standard operating procedures, daily maintenance, weekly maintenance, and internal quality control procedures for the analyzer were strictly adhered. Similarly, during the coagulation test, strict adherence to the standard operating procedures and internal quality control procedures of the Genrui Coagulation Analyzer was consistently upheld. Adherence to specified conditions, such as temperature, time, and guidelines for sample-reagent mixing, was meticulously followed. The reliability of serological test results has been ensured with known positive and negative samples for each test category. The presence of a control line adjacent to the sample line was duly verified. Giemsa quality used for malaria examination was checked with 1 + and 2 + plasmodium-positive samples. Over all research activity processed based on university of Gondar research guideline[38].

Data processing and analysis

Data were collected, coded, entered, and cleaned using EpiData version 4.6, and then transferred to SPSS version 25 for analysis. Descriptive statistics, including percentages, means, medians, interquartile ranges (IQR), and standard deviations (SD), were calculated and presented with tables and graphs. The normality of each dataset was assessed using the Kolmogorov–Smirnov test. Coagulation parameters were compared among chemotherapy-experienced breast cancer patients, chemotherapy-naive breast cancer patients, and healthy controls. A one-way ANOVA test was applied for normally distributed data, while the Kruskal–Wallis H test was used for skewed data. Furthermore, Post hoc analysis was performed for multiple comparisons. Statistical significance was considered at $P < 0.05$.

Results

Socio-demographic and clinical characteristics

A comparative study, with age and sex-matched participants, was conducted involving a total of 180 individuals. The median age ± IQR of the study participants was 40 ± 10, 39.5 ± 11, and 40 ± 7 years for chemotherapy-experienced, chemotherapy-naïve, and healthy controls, respectively. Regarding education, majority of participants in the case groups, specifically 58.3% of chemotherapy-experienced patients and 45% of chemotherapy-naïve patients, were unable to read and write. In contrast, among healthy controls, the predominant educational level was diploma and above, accounting for 63.3% (Table 1). The predominant disease stage was stage III, encompassing 54.2% of patients, followed by stage II, and covering 26.7% of all breast cancer patients. Among chemotherapy-experienced patients, 63.3% were prescribed the Adriamycin Cyclophosphamide type of drug, while Paclitaxel was taken by 28.3% of chemotherapy-experienced participants (Table 1).

Characteristics	Chemotherapy-experienced patients N (%)	Chemotherapy-naïve patients N (%)	Healthy controls N (%)
Sex			
Male	–	–	–
Female	60 (100)	60 (100)	60 (100)
Age			
≤ 40	41 (68.3)	33 (55)	30 (50)
> 40	19 (31.7)	27 (45.0)	30 (50.0)
Residence			
Urban	22 (36.7)	35 (58.3)	49 (81.7)
Rural	38 (63.3)	25 (41.7)	11(18.3)
Educational status			
Not read & write	35 (58.3)	27 (45)	5 (8.3)
1° education	12 (20)	18 (30)	7 (11.7)
2° education	4 (6.7)	8 (13.3)	10 (16.7)
Diploma & above	9 (15)	7 (11.7)	38 (63.3)
Marital status			
Single	8 (13.3)	10 (16.7)	7 (11.7)
Married	47 (78.3)	43 (71.7)	52 (86.7)
Divorced	5 (8.3)	7 (11.7)	1 (1.7)
Occupation			
Farmer	9 (15)	9 (15)	3 (5)
Housewife	31 (51.7)	25 (41.7)	5 (8.3)
Merchant	6 (10)	12 (20)	13 (21.7)
Employed	14 (23.3)	14 (23.3)	39 (65)
Menopausal status			
Menopause	20 (33.9)	20 (33.3)	14 (23.3)
Not menopause	39 (66.1)	40 (66.7)	46 (76.7)
Site of cancer			
Left breast	22 (36.7)	34 (56.7)	–
Right breast	36 (60)	25 (41.7)	–
Both breast	2 (3.3)	1 (1.7)	–
Stage of disease			
I & II	13 (21.7)	21 (35.0)	–
III	35 (58.3)	30 (50)	–
IV	12 (20)	9 (15)	–
Treatment cycle			
4–6	53 (88.3)	–	–
7–8	7 (11.7)	–	–
Drug regimen			
AC based	38 (63.3)	–	–
CMF based	5 (8.3)	–	–
Paclitaxel	17 (28.3)		

Table 1. Socio-demographic and Clinical characteristics of study participants at the UoG-CSH and FHCSH cancer treatment center, Northwest Ethiopia (N = 180), 2023. 1°: primary school, 2°: secondary School AC: Adriamycin Cyclophosphamide, CMF: Cyclophosphamide Methotrexate 5-Fu.

Coagulation parameters of the study participants

The PT and aPTT data showed skewed distributions. Among chemotherapy-experienced, chemotherapy-naive breast cancer patients, and healthy controls, the median PT values were 15, 15.3, and 13.2 s, respectively, indicating significant variations among the groups (p-value: < 0.001). Similarly, the median aPTT values for chemotherapy-experienced, chemotherapy-naive breast cancer patients, and healthy controls were 34.3, 35, and 29.2 s, respectively, with statistically significant differences among the groups (p-value: 0.016). Both PT and aPTT median values were notably higher in chemotherapy-experienced and chemotherapy-naive breast cancer patients compared to healthy controls (Table 2).

The platelet counts and MPV data followed normal distributions, while PDW data showed an abnormal distribution. The mean platelet counts for chemotherapy-experienced, chemotherapy-naive breast cancer patients, and healthy controls were 351.3, 345.6, and 284.3, respectively, with significant differences among the groups (p-values: < 0.001). Similarly, the mean MPV for chemotherapy-experienced, chemotherapy-naive breast cancer patients, and healthy controls were 10.4, 9.5, and 9.0 FL, respectively, with significant differences among the groups (p-values: 0.003) (Table 2).

Most coagulation profiles are significantly elevated in chemotherapy-experienced breast cancer patients and chemotherapy naïve breast cancer patients compared to healthy controls. Parameters such as PT, aPTT, platelet counts and MPV are statistically higher in case groups than controls (Fig. 4).

Multiple comparisons of coagulation parameters among study groups

The median difference in PT showed statistically significant difference between chemotherapy-experienced breast cancer patients and healthy controls, with p-values of < 0.001. Similarly, the median difference in aPTT between chemotherapy-experienced patients and healthy controls was statistically significant, with p-values of 0.019 (Table 3).

Moreover, the difference in mean PLT count between chemotherapy-experienced patients and healthy controls was statistically significant, demonstrating a p-value of 0.001. Similarly, the difference in mean MPV between chemotherapy-experienced patients and healthy controls was statistically significant, with a p-value of 0.002 (Table 3).

Abnormal coagulation parameters in breast cancer patients

In chemotherapy-experienced breast cancer patients, 23 out of 60 participants (38.3%) showed abnormally prolonged aPTT values, while 40 out of 60 participants (66.7%) exhibited abnormally prolonged PT values. Similarly, among chemotherapy-naïve breast cancer patients, 26 out of 60 participants (43.3%) had abnormally prolonged aPTT values, and 47 out of 60 participants (78.3%) displayed abnormally prolonged PT values (Table 4).

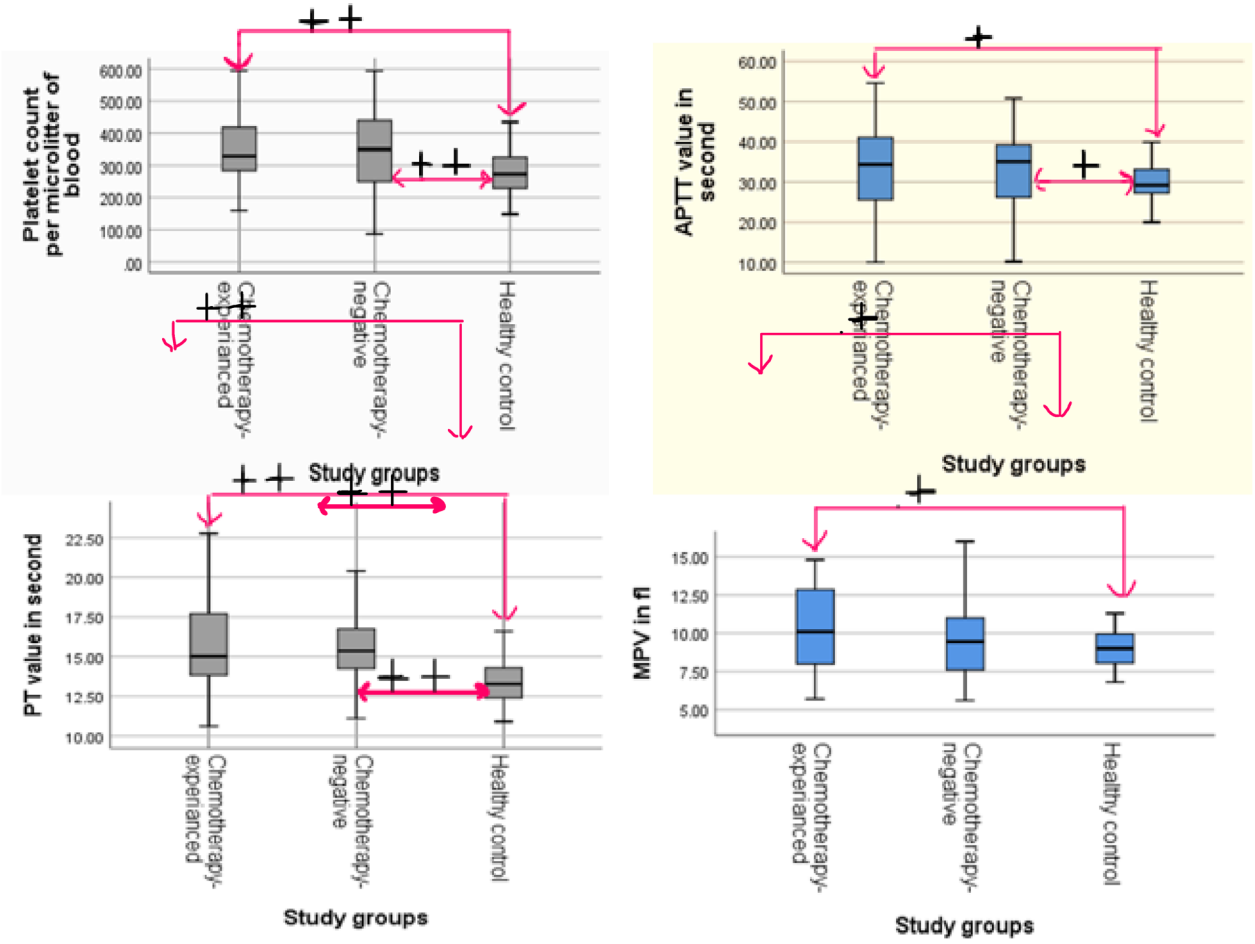
Discussion

Cancer disrupts physiological systems like haemostasis and vascular endothelial functions, increasing the risk of thrombosis[3]. Thrombosis is a prevalent complication and the second-leading cause of mortality in breast cancer patients[23]. Breast cancer is closely associated with hypercoagulation and platelet activation, leading to thrombus formation and an increased risk of haemorrhages due to heightened consumption of clotting factors[39]. This imbalance in procoagulant and anticoagulant processes may alter blood coagulation markers (aPTT, PT, PLT count, and MPV) in breast cancer patients. This study aims to assess coagulation parameters in breast cancer patients and compare them with healthy controls.

The present study revealed a statistically significant increase in median aPTT values in chemotherapy-naïve breast cancer patients compared to healthy controls ($p = 0.009$). The prolonged aPTT observed in chemotherapy-naïve breast cancer patients is likely attributable to DIC, which is characterized by widespread activation of the clotting cascade, leading to the formation of microthrombi, consumption of clotting factors, and resulting in both excessive clotting and bleeding tendencies that prolong aPTT[40,41]. The primary mechanism of thrombosis formation involves the shedding of microparticles containing phosphatidylserine by circulating tumour cells, which provides a negatively charged surface supporting the assembly of coagulation complexes[42,43]. Cancer

Parameters	Chemotherapy-experienced patients		Chemotherapy-naïve patients		Healthy controls		Reference range	*P*-value
	Mean ± SD	Median (IQR)	Mean ± SD	Median (IQR)	Mean ± SD	Median (IQR)		
PLT (10^3/μl)	351.3 ± 99.6	–	345.6 ± 117.5	–	284.3 ± 79.3	–	**90–399**	< 0.001*
MPV (FL)	10.4 ± 2.7	–	9.5 ± 2.4	–	9.0 ± 1.2	–	**8–12.3**	0.003*
PDW (FL)	–	14.9 (2.9)	–	14.9 (4.0)	–	14.5 (4.3)	**10–17.9**	0.260
aPTT (sec)	–	34.3 (15.8)	–	35.0 (13.3)	–	29.2 (5.9)	**26–36**	0.016*
PT (sec)	–	15.0 (3.9)	–	15.3 (2.5)	–	13.2 (1.9)	**11–14**	< 0.001*

Table 2. Comparison of coagulation parameters of study participants at the UoG-CSH and FHCSH cancer treatment center, Northwest Ethiopia (N = 180), 2023. *aPTT* activated partial thromboplastin time, *PT* prothrombin time, *PLT* platelet count, *MPV* mean platelet volume, *PDW* platelet distribution width, *FL* Femto-litters, sec: seconds, *SD* standard deviation, *IQR* inter quartile range. *Indicates statistically significant at p-value < 0.05. Significant values are in (bold).



Note: + indicates statistically significant at p-value <0.05

Note: ++ indicates statistically significant at p-value <0.005

Fig. 4. shown that there is a statistically significant difference in the coagulation parameters of chemotherapy-experienced patients, chemotherapy-negative patients, and healthy controls, as determined by a one-way ANOVA test at the UoG-CSH and FHCSH cancer treatment centers, Northwest Ethiopia, 2023.

cells also generate a cancer procoagulant, a cysteine protease that triggers direct activation of factor X[39]. In addition to DIC, advanced breast cancer can directly affect liver function through metastasis, reducing the synthesis of clotting factors and leading to factor deficiencies that prolong aPTT[44]. Furthermore, some breast cancer patients may develop antiphospholipid antibodies, including lupus anticoagulant, which can also cause prolonged aPTT[45]. Prolonged aPTT can signal an increased risk of bleeding or the presence of coagulopathy, liver dysfunction, or thrombotic disorders, and it necessitates careful assessment to rule out or manage these conditions in patients[46].

The results of this study are consistent with those of earlier research conducted in India[41], China[47], and United Kingdom[18] all studies demonstrated a significantly higher mean aPTT value among breast cancer patients. Contrary to this observation, a study conducted in Turkey[39] revealed that the mean aPTT of breast cancer patients was significantly lower than healthy controls. The possible reason for this may be the stage of the disease in the participants. On the other hand, studies in Pakistan[48], and India[49] have shown that the difference in mean aPTT between breast cancer patients and healthy controls was not statistically significant. The variation between these findings and our study might be attributed to differences in study design, population demographics, sample sizes, methodological variations in laboratory analyses, and differences in the timing of cancer diagnosis.

In current study, the median aPTT values in breast cancer patients who have undergone chemotherapy are significantly elevated compared to healthy controls ($p = 0.019$). In addition to cancer cells, chemotherapy drugs increase the risk of thrombosis by inducing endothelial cell apoptosis, releasing endothelial-derived procoagulants

Parameters	Grouping variable(I)	Grouping variable(J)	Sig.
PLT	Chemotherapy naïve	Chemotherapy experienced	0.948
		Healthy Control	0.003*
	Chemotherapy experienced	Healthy Control	0.001*
MPV	Chemotherapy naïve	Chemotherapy experienced	0.100
		Healthy Control	0.342
	Chemotherapy experienced	Healthy Control	0.002*
aPTT	Chemotherapy naïve	Chemotherapy experienced	0.715
		Healthy Control	0.009*
	Chemotherapy experienced	Healthy Control	0.019*
PT	Chemotherapy naïve	Chemotherapy experienced	0.659
		Healthy Control	< 0.001*
	Chemotherapy experienced	Healthy Control	< 0.001*

Table 3. Multiple comparisons of coagulation parameters among study groups at the UoG-CSH and FHCSH cancer treatment center, Northwest Ethiopia (N = 180), 2023. *aPTT* activated partial thromboplastin time, *PT* prothrombin time, *PLT* platelet count, *MPV* mean platelet volume, *PDW* platelet distribution width. *indicates statistically significant at *p*-value < 0.05.

Parameters	Chemotherapy Experienced N (%)	Chemotherapy Naive N (%)	Reference range
aPTT			
Short	16 (26.7)	15 (25)	26–36
Normal	21 (35)	19 (31.7)	
Prolonged	23 (38.3)	26 (43.3)	
PT			
Short	1 (1.7)	0	11–14
Normal	19 (31.7)	13 (21.7)	
Prolonged	40 (66.7)	47 (78.3)	
PLT			
Thrombocytopenia	–	1	90–399
Normal	44 (73.3)	41 (68.3)	
Thrombocytosis	16 (26.7)	18 (30)	
MPV			
Low	16 (26.7)	18 (30)	8–12.3
Normal	27 (45)	36 (60)	
High	17(28.3)	6 (10)	
PDW			
Low	7 (11.7)	7 (11.7)	10–17.9
Normal	46 (76.7)	44 (73.3)	
High	7 (11.7)	9 (15)	

Table 4. Abnormal coagulation parameters of breast cancer patients at the UoG-CSH and FHCSH cancer treatment centers, Northwest Ethiopia (N = 120), 2023. *aPTT* activated partial thromboplastin time, *PT* prothrombin time, *PLT* platelet count, *MPV* mean platelet volume, *PDW* platelet distribution width.

and microparticles, and amplifying the release of microparticles and inflammatory cytokines through damage to tumour cells[50,51]. Moreover, the drugs damage hepatocytes, resulting decline of natural anticoagulant production such as antithrombin III, heparin cofactor II, protein C, protein S, and thrombomodulin[50,51]. Chemotherapy drugs such as cyclophosphamide and doxorubicin can also disrupt gut bacteria and liver function, potentially leading to vitamin K deficiency, which impairs the synthesis of clotting factors like II, VII, IX, and X, thereby prolonging aPTT[52]. Additionally, certain chemotherapy agents may induce bone marrow suppression or alter coagulation factor production, leading to an imbalance in the coagulation cascade, which can contribute to prolonged aPTT[53]. Prolonged aPTT in chemotherapy-experienced patients may serve as an early indicator of chemotherapy-induced coagulopathy, which may necessitate closer monitoring and interventions to prevent serious bleeding or thrombotic complications[54].

In line with our study, a study conducted in United Kingdom[18] revealed that the mean aPTT value of chemotherapy experienced patients was significantly elevated compared to healthy controls. On the other hand, a study conducted in China[47] shown that mean aPTT of chemotherapy experienced breast cancer patients was

comparable to healthy controls. The possible reason for the outcome difference between our study and China might be related to the variation in treatment cycle and drug regimen.

Our study found that chemotherapy-naïve breast cancer patients exhibit statistically higher median PT values than healthy controls ($P<0.001$). The prolonged PT values in breast cancer patients may be due to the overutilization of coagulation factors during thrombosis formation, such as arterial thrombosis, venous thrombosis, and DICs[41]. The extrinsic pathway of blood coagulation is activated with TFs expressed by cancer cells, leading to thrombin generation[39]. Tumour cells also shed microparticles with active TFs on their surfaces, contributing to thrombin generation, and thrombin, in turn, converts fibrinogen to fibrin[42,43]. Moreover, prolonged PT values can occur due to liver dysfunction associated with metastasis, vitamin K deficiency, autoimmune disorders, coagulopathies like DIC, or the presence of other underlying health conditions[55]. Monitoring and addressing these factors is critical for managing bleeding risks and ensuring the overall health of these patients and if a prolonged PT is identified, further tests such as liver function tests, coagulation factor assays, and screening for DIC or autoimmune conditions should be performed to pinpoint the cause and guide treatment[55].

The current study results align with those of studies conducted in India[41], Turkey[39], Pakistan[48], and United Kingdom[18] all of those demonstrated that the mean PT values of breast cancer patients were statistically higher compared to healthy controls. Conversely, studies conducted in India[49], and China[47] reported, that the difference in mean PT value between breast cancer patients and healthy controls was not statistically significant. The variation between our study results and others may be attributed to the stage of disease and difference in sample size.

Chemotherapy-experienced breast cancer patients, like their chemotherapy-naïve counterparts, demonstrate statistically higher median PT values than healthy controls ($P<0.001$). Chemotherapy drugs can induce prolonged PT through several mechanisms such as; increase the consumption of coagulation factors by boost the release of tumour-derived TF, TF-containing microparticles, and inflammatory cytokines by damaging cancer cells[50,51]. Many chemotherapy drugs can cause liver toxicity directly, and chemotherapy-induced liver dysfunction can reduce the production of clotting factors, leading to a prolonged PT[56]. Chemotherapy agents also can induce systemic inflammation and oxidative stress, disrupting the balance between procoagulant and anticoagulant factors. This imbalance can alter clotting factor activity or increase their consumption, potentially leading to a prolonged PT[57]. The prolonged PT may indicate several underlying issues, including liver dysfunction, vitamin K deficiency, coagulopathies, or chemotherapy-induced toxicity[58]. Effective management requires close monitoring, timely intervention with clotting factor replacement, adjustments to chemotherapy doses, and ensuring the patient's safety during invasive procedures[58].

In line with our research, a study in the United Kingdom[18] found a significantly higher mean PT value in chemotherapy-experienced patients compared to healthy controls. However, a study in China[47] reported that the mean PT of chemotherapy-experienced breast cancer patients was similar to healthy controls. The differences in outcomes between our study and the Chinese study could be attributed to various factors, such as variations in study population, treatment cycles, and drug regimens.

This study identifies a notable thrombocytosis in chemotherapy-naive breast cancer patients, with a prevalence of 30%. Furthermore, the mean platelet count in chemotherapy-naive patients is significantly elevated ($P=0.003$) compared to healthy controls. The mechanisms by which cancer cells contribute to thrombocytosis in breast cancer are complex and unclear. However, one highlighted factor is the continual compensation for DIC. Breast cancer cells are recognized for their continuous coagulation activation, leading to the on-going consumption of platelets. This consumption triggers increased thrombopoiesis, ultimately causing thrombocytosis[22,23]. In addition, thrombocytosis can result from tumor-driven inflammatory responses, cytokine secretion, hypoxia, and the potential direct production of platelet-stimulating factors by the tumor itself, with elevated platelet counts also serving as a compensatory mechanism to address bleeding risks or hypoxia[59]. Thrombocytosis can indicate an underlying systemic inflammatory response or tumor progression and is associated with an increased risk of thromboembolic events, bleeding, and metastasis. So early detection and regular monitoring of platelet counts, along with an assessment of underlying causes, are essential for guiding therapeutic decisions and improving patient outcomes[60].

The current study's findings align with those studies conducted in the Ethiopia[61], India[41], Turkey[39], and United Kingdom[18] all of those studies reported significant thrombocytosis in breast cancer patients. In contrast to our study, studies in Egypt[62], and Poland[63] found that the mean PLT count in breast cancer patients was significantly lower than healthy controls. The possible reason for this may be the stage of the disease in the participants. On the other hand, studies in Turkey[64], and India[49] found no statistically significant difference in platelet count between breast cancer patients and healthy controls. This disparity may be attributed to differences in the time of diagnosis, unmatched age of study groups, disease stage and differences in study design.

Concurrently, in tandem with chemotherapy-naïve patients, individuals who have undergone chemotherapy for breast cancer demonstrate a noteworthy incidence of thrombocytosis, with a prevalence of 26.7%. Moreover, the mean PLT count in chemotherapy-experienced patients exhibits a statistically significant elevation ($p=0.001$) in comparison to a healthy control. The intricate mechanisms by which chemotherapy drugs impact thrombocytosis in breast cancer patients involve complex processes. Chemotherapy induces an inflammatory response linked to changes in platelet levels. Inflammatory cytokines and mediators stimulate platelet production and release from the bone marrow[65]. Moreover, chemotherapy drugs can suppress bone marrow function, leading to a compensatory increase in platelet production as the body attempts to restore normal blood cell levels[66]. In chemotherapy-experienced breast cancer patients, thrombocytosis can significantly impact both cancer treatment and overall management. It is associated with an increased risk of thromboembolic events, metastasis, and chemotherapy-related complications. Early detection, regular monitoring, and tailored interventions are essential for effectively managing thrombocytosis and ensuring optimal patient outcomes[67].

In line with our study, the studies conducted in United Kingdom[18], and Poland[63] indicated that the mean PLT count in chemotherapy-experienced patients was significantly elevated compared to healthy controls.

This study revealed that mean MPV in chemotherapy-experienced breast cancer patients was significantly higher compared to healthy controls ($P = 0.002$), with the prevalence of abnormally elevated MPV at 28.3%. The likely mechanism behind this elevation in MPV among chemotherapy-experienced breast cancer patients may involve drug-induced inflammation. Chemotherapy drugs increase proinflammatory cytokine secretion, including interleukins IL-1, IL-3, and IL-6, which in turn stimulates megakaryocyte proliferation and results in an elevated presence of large platelets[68]. In addition, elevated MPV in breast cancer patients is linked to ongoing platelet activation, with tumour cell-induced platelet aggregation through direct contact or mediators like adenosine diphosphate, thromboxane A2, or serine proteinases and generation of matrix metalloproteinase by cancer cells[23]. A study conducted in Poland[63] reported a statistically significant elevation in MPV among breast cancer patients undergoing chemotherapy, aligning with the observations made in the present study.

Strength and limitations of the study

The multicenter design of the study significantly enhances its findings, providing robust evidence on breast cancer and coagulopathy. However, limitations include the exclusion of key coagulation parameters like fibrinogen and D-dimer. Fibrinogen and D-dimer are vital for evaluating coagulation disorders, and their absence may restrict a comprehensive understanding of the link between breast cancer and coagulopathy. These parameters are more sensitive than others in detecting coagulopathy within the system. Therefore, omitting them would hinder the ability to clearly understand how cancer and chemotherapy influence the coagulation profiles of patients. In addition, manual sample transportation and processing are also considered limitations.

Conclusions and recommendation

Significantly elevated PLT count, aPTT, and PT values were detected in both chemotherapy-experienced and chemotherapy-naïve breast cancer patients compared to healthy controls. Specifically, there were notable elevations in the mean PLT count, median aPTT, and median PT values in chemotherapy-naïve breast cancer patients compared to healthy controls. Similarly, significant elevations were observed in the mean PLT count, mean MPV, median aPTT, and median PT values in chemotherapy-experienced breast cancer patients compared to healthy controls. These findings provide evidence for the existence of coagulopathy in breast cancer patients. Therefore, coagulation profile tests are crucial for the early detection and diagnosis of coagulopathies such as thrombosis and hemorrhage, which are significant comorbidities that negatively affect patient survival. Early detection and diagnosis of coagulopathy are critical for improving patient outcomes, making it advisable to include tests such as aPTT, PT, and platelet parameter analysis as routine laboratory tests for breast cancer patient managements. However, no significant differences in coagulation parameters were found between chemotherapy-naïve and chemotherapy-experienced breast cancer patients.

Based on our study findings, we strongly recommend that future research conduct more extensive longitudinal studies to address the limitations of this study. Additionally, monitoring changes in coagulopathy over time by incorporating tests such as fibrinogen, D-dimer, and other related biochemical markers would provide valuable insights.

Data availability

All data generated or analyzed during this study are included in the manuscript.

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Author contributions

S.A. involved in study design, proposal writing, data collection and analysis, result interpretation, and manuscript writing and reading. E.S. involved in study design, proposal writing, supervise data collection, analysis and interpretation, manuscript writing, and reading. M.A. involved in study design, supervise data collection and data analysis, result interpretation, and manuscript writing and reading. T.A. involved in study design, proposal writing, manuscript reading and aproving.

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Declarations

Competing interests

The authors declare no competing interests.

Ethical approval and consent to participate

The study was conducted after reviewed and approved by the ethical review committee of the School of Biomedical and Laboratory Sciences, College of Medicine and Health Sciences, University of Gondar with (Reference No. SBMLS/514). Moreover, letter of support was submitted to the UoG-CSH and FHCSH. Before starting the actual data collection, permission was obtained from both Hospitals Chief Executive Officer. Additionally, after explaining the purpose, benefits, and the possible risks of the study, written informed consent from the age of 18 and above and/or assent from those less than 18 years old study participants along with written informed consent from their respective parents/caregiver/guardians was obtained. And also, written informed consent from illiterate study participants was obtained from their respective parents/guardians. All laboratory results were kept confidential. Since those were stored in a file using codes without study participant's name. Apparently healthy participants, those positive for parasites, abnormal coagulation profiles, and platelet count were linked to the hospitals for appropriate treatment and management. All methods were carried out in accordance with relevant guidelines and regulations.

Additional information

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