

# The Prevalence of Coagulopathy and Associated Factors Among Adult Type II Diabetes Mellitus Patients Attending the University of Gondar Comprehensive Specialized Hospital, Northwest Ethiopia

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**Introduction:** Diabetes mellitus is a heterogeneous disorder of metabolism which results hyperglycemic-related atherothrombotic complications. These complications are the leading cause of death in diabetes mellitus patients. Therefore, this study was aimed to determine the prevalence of coagulopathy and associated factors among adult type II diabetes mellitus patients attending at University of Gondar comprehensive specialized hospital.

**Methods:** A facility-based cross-sectional study was conducted among 357 study participants. A questionnaire and a data collection sheet were used to collect the sociodemographic and clinical data, respectively. About 6mL of venous blood samples were collected for coagulation tests and complete blood count. For prolonged coagulation tests, a mixing test was performed. Data were entered into EpiInfo and exported to SPSS for statistical analysis. Then, descriptive statistics were done. A binary and multivariable logistic regression model was used to identify the associated factors. P-value <0.05 was considered as statistically significant.

**Results:** In this study, 357 study participants were included. Of them, 52.1% (186) and 80.7% (288) were females and urban residences, respectively. The prevalence of coagulopathy was 26.6% (95% CI: 22.1, 31.5%). Out of this, 12.3% and 8.7% showed shortened PT and aPTT, respectively. In addition, the prevalence of prolonged PT and aPTT were 5.6% and 3.9%, respectively. From the prolonged PT and aPTT, the prevalence of factor deficiency was 95% and 92.8%, respectively. Being female (AOR = 2.06; 95% CI: 1.11–3.85%), abnormal BMI (AOR = 1.94; 95% CI: 1.08–3.50), and educational status of high school (AOR = 0.26; 95% CI: 0.10–0.83%) were significantly associated with hypercoagulation.

**Conclusion:** Coagulopathy is an important public health problem among type II diabetes mellitus patients. Being female and having abnormal BMI were associated with hypercoagulation. Therefore, regular monitoring of coagulation parameters is vital to reduce the consequence of coagulopathy.

**Keywords:** coagulopathy, mixing study, type II diabetes mellitus, Gondar, Ethiopia

## Background

Diabetes Mellitus (DM) is a group of diseases that is described by hyperglycemia state which arises due to failure of insulin production, action, or both.<sup>1</sup> Diabetes mellitus is etiologically categorized into two types: type I and type II.<sup>2</sup> Type I DM accounts for 5–10% of all diabetes cases and is characterized by the destruction of insulin-producing  $\beta$ -cell of the islets of the pancreas by an autoimmune reaction.<sup>3</sup> There is a complete insufficiency of insulin in type I DM. Type I DM

is usually seen in children but it can also arise at any age.<sup>4</sup> Type II DM (T2DM) is the major type of diabetes, corresponding to 90–95% of all cases of diabetes worldwide.<sup>5</sup>

The chronic hyperglycemia state in DM affects various stages of coagulation such as clot formation, platelet activation, endothelial cell function, and fibrinolysis.<sup>6</sup> Type II DM is related to a quantitative increase in platelet surface proteins such as Glycoprotein Ib (GPIb) and GPIIb/IIIa molecules.<sup>7</sup> All changes result in the initiation of thrombus formation.<sup>8</sup> Abnormally prolonged activated Partial Thromboplastin Time (aPTT) and/or Prothrombin Time (PT) tests may result from the clotting factor deficiency or presence of pathological factor inhibitors.<sup>9</sup> Pathological coagulation factor inhibitors are usually antibodies that attach and neutralize pro-coagulant molecules.<sup>10</sup> These pathological inhibitors can be specific or non-specific.<sup>11</sup>

Eighty percent of T2DM deaths are caused by thrombotic death, of which 75% are caused by cardiovascular incidents.<sup>12</sup> Atherothrombotic complications are the leading cause of death in DM patients. Studies revealed that being female, old age, duration of T2DM, obesity, and poor glycemic control were also associated with the development of hypercoagulation.<sup>13,14</sup> Hence, the PT test is used to screening and assesses disorders involving factors from the extrinsic and common coagulation pathway (Factor I, II, V, VII, and X).<sup>15</sup> Whereas, aPTT is used to screen coagulation factors from the intrinsic and common coagulation pathways like factors I, II, V, VIII, IX, XI, and XII.<sup>16</sup> Further, the mixing test is also an important indicator of the presence of clotting factor deficiency or the presence of pathological coagulation inhibitors.<sup>17</sup> It is performed by mixing equal amount of patient plasma with Normal Pooled Plasma (NPP) and correction of coagulation time was measured.<sup>18</sup>

Diabetes mellitus is a main public health concern across the world that affects millions of people each year.<sup>19</sup> Conforming to the 2019 International Diabetic Federation (IDF) report globally, an estimated 463 million adults are living with DM in the age group of 20–79 years. The IDF also reported that in 2019 about 4.2 million people died in the age group of 20–79 years.<sup>20,21</sup> In Africa, the prevalence is approximately 19.4 million adults aged 20–79 years. Death due to diabetes in Africa region is reported to be 366,200.<sup>20,21</sup> In Ethiopia, it is estimated that 1,699,400 adults or 3.2% of the adult population are living with diabetes.<sup>22</sup> A study conducted in Ethiopia showed that, about 58.8% of T2DM individuals have a hemostatic abnormality.<sup>23</sup> A related study also found that in untreated cases of DM, aPTT is shortened relative to treated DM patients and non-diabetic patients.<sup>24</sup>

Even though there were limited studies conducted on the coagulopathies among T2DM patients, most of the studies were comparative cross-sectional with small sample sizes. Moreover, the results have been inconsistent and factors associated with coagulopathies were not studied well. Therefore, this study aims to determine the prevalence of coagulopathy and associated risk factors among T2DM patients. This study also tried to differentiate the presence of clotting factor deficiency or pathological factor inhibitors through a mixing test.

## Materials and Methods

### Study Setting and Study Population

A hospital-based cross-sectional study was used to determine the prevalence of coagulopathy and associated factors among adult T2DM patients. This study was conducted at the University of Gondar Comprehensive Specialized Hospital (UoGCSH) from March to June 2021. The hospital is found in Gondar town which is 737 km away from Addis Ababa, the capital city of Ethiopia. According to the 2007 Ethiopian census report, Gondar town has a total population of 207,044, and more than half (108,924) of them are females.<sup>25</sup> The population of Gondar town in 2021 is estimated to be 378,000.<sup>26</sup> The hospital is providing different medical services to more than 7 million people in the region and people of the neighboring region.

### Inclusion Criteria

A total of 357 study participants were included. All adult T2DM patients that attend the chronic illness clinic of the UoGCSH and willing to participate in this study were included.

## Exclusion Criteria

Study participants taking antithrombotic agents like warfarin, heparin, and aspirin within 10 days before sample collection, patients who had undergone a recent surgical procedure, history of venous thromboembolism, patients with known inherited coagulation disorders, cancer, hyperthyroidism, and severely ill patients were excluded from the study.

## Operational Definitions

**Coagulopathy:** A prolonged or shorted PT and/or aPTT values out of the accepted reference range or abnormality in platelet count number.<sup>27</sup>

**Hypercoagulation:** Shortening of PT and/or aPTT results and an increase in platelet count.<sup>12</sup>

**Normal platelet count:** The normal platelet count in adults is between 150,000 and 450,000/ $\mu$ L.<sup>28</sup>

**Normal time for PT:** The normal time for PT in adults is between 10 and 16 seconds.<sup>29</sup>

**Normal time for aPTT:** The normal time for aPTT in adults is 24–36 seconds.<sup>29</sup>

**Anemia:** Anemia in an adult is defined as a hemoglobin level of <12g/dL for Females and <13g/dL for Males.<sup>30</sup>

## Data Collection Procedure

### Sociodemographic Characteristics and Behavioral Data Collection

A semi-structured and pretested questionnaire was used to collect sociodemographic and behavioral data from eligible diabetic patients. The questionnaire was used to make face to face interviews with the participants. The sociodemographic data that were included were age, sex, occupation, residence, and level of education. Behavioral data such as the habit of regular physical exercise and cigarette smoking were collected using questionnaire with a face-to-face interview by trained nurses working in the chronic illness clinic of the UoGCSH.

### Clinical Data Collection

Clinical data including duration of DM, duration of antidiabetic drug intake, blood Pressure, and other related data were collected by trained nurses from the patient's medical chart using data collection sheets. The weight and height of the study participants were measured and were used for the calculation of Body Mass Index (BMI).

**Body Mass Index:** The BMI is calculated after careful measurement of the weight and height of the study participants. The formula used for calculating BMI is weight in kg divided by height in meter square.

### Blood Sample Collection

About 6 milliliters of venous blood samples were collected using the vacutainer method. About 3mL of blood was collected to a tube containing tri-potassium Ethylene Diamine Tetra acetic Acid (EDTA) and 2.7mL of blood was collected to a tube that contains 0.3mL of 3.2% sodium citrate. The EDTA anticoagulated blood was used for Complete Blood Count (CBC) tests and peripheral blood film. The sodium citrate anticoagulated blood was used for PT, aPTT, and mixing tests.

## Laboratory Processing

**Platelet poor plasma preparation:** A Platelet Poor Plasma (PPP) was prepared from all study participants. The PPP was prepared from the sodium citrate anticoagulated blood sample. The sodium citrate anticoagulated whole blood sample was centrifuged at 1500g for 15 minutes.<sup>31</sup>

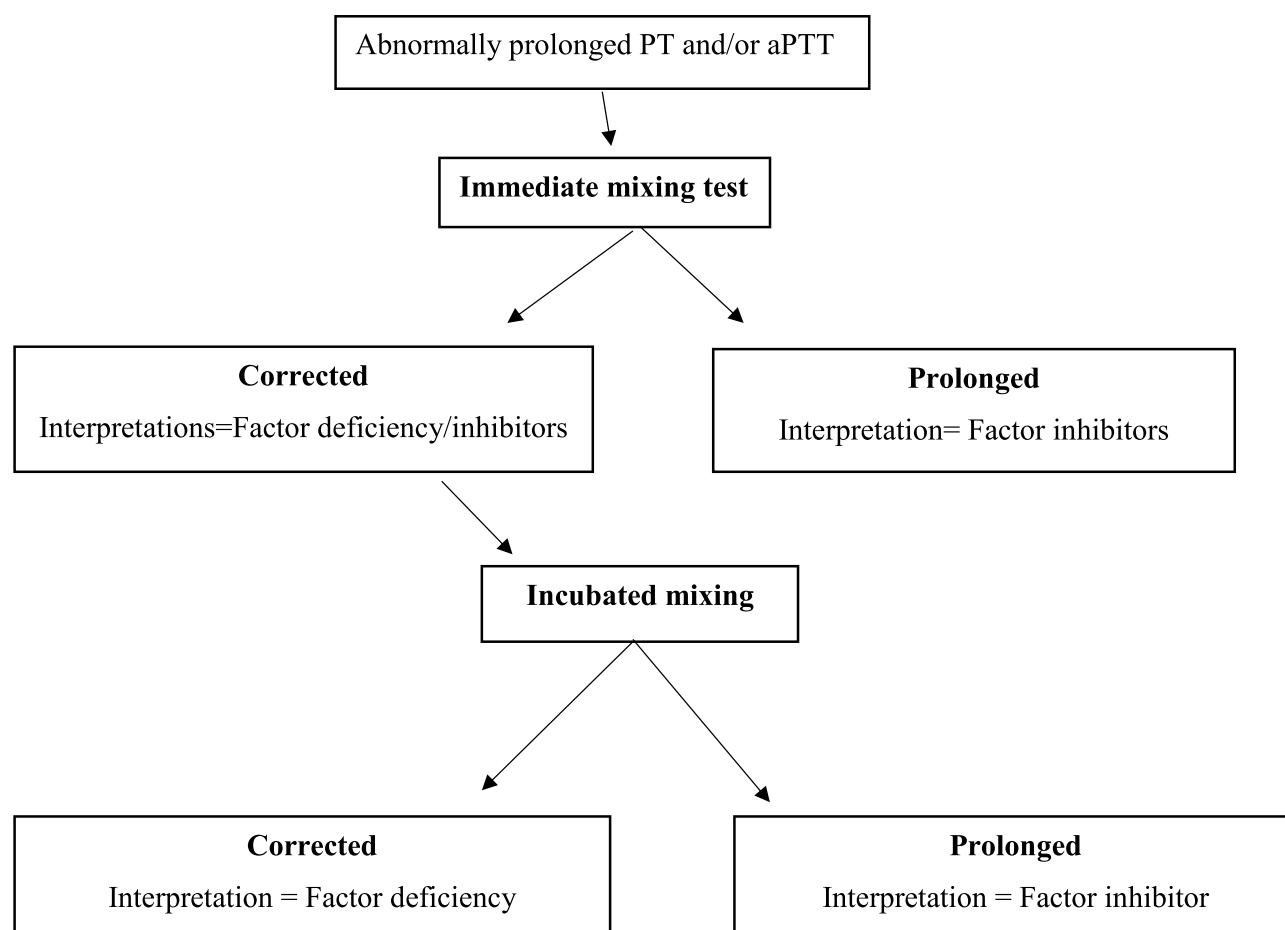
**Platelet count:** The Beckman Coulter UniCel DxH 800 fully automated hematology analyzer was used to determine the CBC result. The coulter principle is used in the DxH 800 CBC analyzer. A small opening (aperture) between electrodes is the sensing zone through which suspended particles pass. Coulter measures the displaced volume as a voltage pulse, the height of each pulse being proportional to the volume of the cell and frequency of electrical pulse being proportional to cell count. The system counts the individual cells and provides cell size distribution. The COULTER VCS (Volume, Conductivity, and Scatter) established WBC differential technology using three measurements: individual cell volume, high-frequency conductivity, and laser-light scatter.

PT and aPTT test: - The coagulation profile test was carried out by using a HUMACLOT DUE PLUS coagulation analyzer which uses the turbidity meter principle. The principle of PT is coagulation system stimulation in a plasma in the presence of tissue factors (Apo protein and Phospholipid) and  $\text{CaCl}_2$ . This leads to stable clot development. The time from activation to the formation of a stable clot is recorded in seconds.<sup>32</sup> The principle of aPTT test is coagulation system activation in a plasma sample in the presence of a platelet substitute (silica), an activator of factor XII, and  $\text{CaCl}_2$ . This leads to a stable clot being formed. The time from activation to the formation of a stable clot is recorded in seconds and represents the aPTT.<sup>33</sup>

Mixing Test: A mixing test was performed by making a 1:1 mixing of the patient's plasma with NPP. In the mixing study, patient plasma with extended aPTT and/or PT is mixed with NPP. After blending the two samples, aPTT and PT are measured. Mixing studies are used to differentiate between possible causes of prolonged screening test results, especially to differentiate between factor deficiency and pathological inhibitor involvement.<sup>34</sup> The mixing study can be performed immediately or after incubation for some time. After mixing test, normalization of result indicates the presence of factor deficiency whereas if the result remains the same it indicates the presence of pathological inhibitors (Figure 1).

## Blood Film Examination for Malaria Parasites

Malaria was diagnosed by using light microscopic examination of a stained venous blood smear (thick and thin blood film) with 10% Giemsa. Thick and thin blood film was prepared on a clean microscope slide. The slide was allowed to air dry and then fixed with methanol. Finally, it was stained with 10% Giemsa stain.<sup>35</sup>



**Figure 1** Algorithm of mixing study for the determination of factor deficiency and pathological factor inhibitors.

## Data Quality Control Measures

### Sociodemographic and Clinical Data Quality Control Measures

The questionnaire was prepared in English and translated to Amharic then converted back to English to check for uniformity. The pretest of the questionnaire was done on 5% of the participants at Maraki Health center. All study participants were informed about the purpose and significance of the study before data collection to make them fully concerned about their response. The collected data were checked daily for consistency and accuracy. Data collection was watchfully supervised by the principal investigator.

### Laboratory Data Quality Control Measures

The quality of the sample was maintained by examining if it met accepted parameters such as hemolysis, clotting, volume, and collection time. After the blood is withdrawn, it was dispensed to the wall of the test tube to avoid hemolysis. Daily temperature monitoring was performed for the refrigerators that hold the sample and the reagents. All reagents were checked for expiry dates and prepared in compliance with the manufacturer's guidelines. The three-level of commercial hematology cell controls (Low, Normal, and High) were run daily. Every day before the samples were examined, an identical normal and abnormal lyophilized sample was utilized for the coagulation test. The quality of the smear and Giemsa stain were checked using known malaria positive and negative slides.

## Statistical Analysis

The data were coded and double entered into Epi info version 7.2.4.0 and then transferred to SPSS version 20 for analysis. Descriptive statistics like frequencies, tables, and figures were used to summarize the characteristics of the study population. The chi-square test was used to determine the significance of the assumed association. The Shapiro–Wilks test was used to check for the normality of the data. The Hosmer and Lemeshow test statistics were performed to check for goodness-of-fitness. To determine factors associated with coagulation abnormality in DM patients, bivariable and multivariable logistic regression analysis was used. The odds ratio with its 95% interval was used to determine the strength of association between the predictor and dependent variable. Variables whose P value of less than 0.25 on Bivariable analysis was entered jointly into a multivariable logistic regression analysis. A p-value of less than 0.05 was considered statistically significant.

## Results

### Socio-Demographic Characteristics

A total of 357 study participants were enrolled in this study, with 52.1% (186) of them being female and 80.7% (288) residing in urban. The study participant's mean age was  $54 \pm 12$  years with a range of 23–87 years. The majority of the study participants, 72.0% (257) and 77.3% (276) were 40–64 years old and married, respectively (Table 1).

### Clinical and Behavioral Characteristics

About 43.7% (156) of the study participants had a history of other chronic diseases. Almost all of the study participants, 99.7% (356) were taking an antidiabetic drug. Of the total study participants, 8.7%<sup>31</sup> were anemic. The number of patients with hypertension was 60.5% (216) (Table 2).

### Prevalence of Coagulopathy

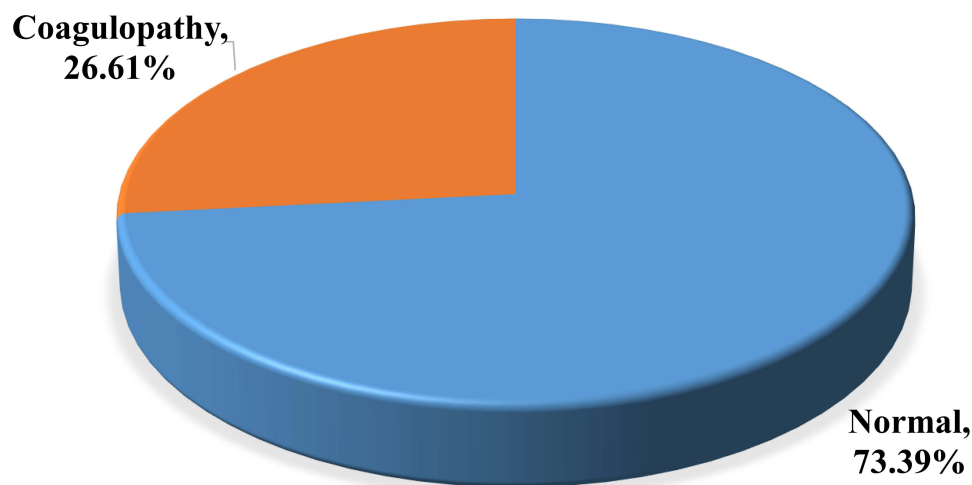
The overall prevalence of coagulopathy was 26.6% (95/357): 17.6% (63/357) showed one of the three coagulopathy, 7.6% (27/357) showed two of the three coagulopathy, and 1.4% (5/357) showed all three coagulopathies. From the total study participants, 12.3% (44/357) showed shortened PT and 8.7% (31/357) showed shortened aPTT. Thrombocytopenia was observed in 5.3% (19/357) of the study participants. In addition to this, the prevalence of prolonged PT tests was 5.6% (20/357) from whom factor deficiency and inhibitors were 95%<sup>19</sup> and 5%,<sup>1</sup> respectively. Whereas, the prevalence of the prolonged aPTT test was 3.9% (14/357) from whom factor deficiency and inhibitors were 92.8%<sup>13</sup> and 7.14%,<sup>1</sup> respectively (Figure 2).

**Table 1** Socio-Demographic Characteristics of Adult T2DM Patients Attending the UoGCSH Chronic Illness Clinic, Northwest Ethiopia, 2021

Sociodemographic Characteristics		Frequency	Percentage
<b>Gender</b>	Male	171	47.9%
	Female	186	52.1%
<b>Age</b>	18–39	34	9.5%
	40–64	257	72.0%
	>65	66	18.5%
<b>Place of residence</b>	Urban	288	80.7%
	Rural	69	19.3%
<b>Educational status</b>	Unable to read and write	97	27.2%
	Elementary	110	30.8%
	High school	90	25.2%
	College and above	60	16.8%
<b>Occupation</b>	Housewife	89	24.9%
	Office work	66	18.5%
	Merchant	61	17.1%
	Farmer	53	14.8%
	In retirement	45	12.6%
	Private	43	12.04%

**Table 2** Clinical and Behavioral Characteristics of Adult T2DM Patients Attending the UoGCSH Chronic Illness Clinic, Northwest Ethiopia, 2021

Clinical and Behavioral Characteristics		Frequency	Percentage
<b>Duration of DM in years</b>	<6	235	65.8%
	≥6	122	34.2%
<b>Antidiabetic drug use status</b>	Yes	356	99.7%
	No	1	0.3%
<b>Duration of antidiabetic drug use in years</b>	<6	236	66.1%
	≥6	121	33.9%
<b>Traditional medicine use</b>	Yes	27	7.6%
	No	330	92.4%
<b>Oral contraceptive use (n=186)</b>	Yes	7	3.8%
	No	179	96.2%
<b>Doing regular physical exercise</b>	Yes	150	42.0%
	No	207	58.0%
<b>Cigarette smoking</b>	Yes	5	1.4%
	No	352	98.6%
<b>History of chronic illness</b>	Yes	156	43.7%
	No	201	56.3%
<b>BMI</b>	Underweight	12	3.4%
	Normal	198	55.5%
	Overweight	147	41.2%
<b>Blood pressure</b>	Hypertensive	216	60.5%
	Normotensive	141	39.5%
<b>Anemia</b>	Anemic	31	8.7%
	Non-anemic	326	91.3%



**Figure 2** The types of coagulopathy identified among T2DM patients.

## Factors Associated with Hypercoagulation

Since hypercoagulation is the most commonly occurring coagulopathy among DM patients, it was selected for the associated factor analysis. Therefore, in bivariable logistic regression analysis, study participants with gender ((COR) = 0.49; 95% CI: 0.27–0.88), educational status (high school, COR = 0.38; 95% CI: 0.14–1.03), physical exercise (COR = 1.42; 95% CI: 0.78–2.55), and BMI (COR = 0.53; 95% CI: 0.30–0.94) showed association with hypercoagulation. Consequently, these variables were subjected to multivariable logistic regression. On the other hand, the study participants' age, residence, history of chronic illness, duration of DM, duration of antidiabetic drug use, and blood pressure did not show any statistically significant association with hypercoagulation.

However, in multivariable analysis, being Female (AOR = 2.06; 95% CI: 1.11–3.85), education status of High school (AOR = 0.26; 95% CI: 0.10–0.83), and BMI (AOR = 1.94; 95% CI: 1.08–3.50) were significantly associated with hypercoagulation. On the other hand, physical exercise did not show any statistically significant association with hypercoagulation (Table 3).

## Discussion

Coagulopathy is an important public health problem among T2DM patients. It is responsible for morbidity and mortality in the world.<sup>36</sup> Identification of T2DM patients with coagulopathy helps to reduce the risk associated with it.<sup>37</sup> The T2DM patients are vulnerable to abnormal platelet count, PT, aPTT, and other coagulation impairments.<sup>38</sup> Furthermore, diabetes mellitus is a pro-coagulant state.<sup>39</sup> Hence, this study aimed to assess the prevalence and associated factors of coagulopathy among adult T2DM patients attending the UoGCSH chronic illness clinic.

In this study, the overall prevalence of coagulopathy was 26.6% (95% CI: 22.1, 31.5%). Coagulopathy in T2DM patients results from hyperglycemia conditions that result in the glycation of hemoglobin, coagulation factors, and other important proteins that are involved in the coagulation cascade.<sup>37</sup> The prevalence of coagulopathy in this study is lower compared to a study conducted by Asrat et al in Ethiopia, which reported a 58.8% prevalence of coagulopathy in the diabetes population (Both type I & II).<sup>40</sup> The possible reasons for these disagreements might be associated with differences in the study population, coagulation parameters studied, the reference range used for the CBC and coagulation tests, the difference in sample size, and the study design used.

In the current study, the prevalence of shortened PT and aPTT were 12.3% (95% CI: 9.10, 16.2%) and 8.7% (95% CI: 6.10, 11.90%), respectively. Shortening of PT and aPTT among T2DM patients is associated with increased platelet surface proteins, plasma coagulation factors, and reduction of natural anticoagulant molecules.<sup>7,8,41–43</sup> The prevalence of shortened PT and aPTT in this study is lower compared to a study conducted by Ebrahim et al in Ethiopia that reported a 16.7% and 63.3% prevalence of shortened PT and aPTT, respectively.<sup>44</sup> The possible reason for this difference might be



**Table 3** Factors Associated with Hypercoagulation Among Adult T2DM Patients

Characteristics	Category	Hypercoagulation		COR(95% CI)	P-value	AOR(95% CI)	P-value
		Yes n(%)	No n(%)				
Gender	Male	19 (11.1%)	152 (88.9%)	1	0.018	2.06 (1.11–3.85)	0.023
	Female	38 (20.4%)	148 (79.6%)	0.49 (0.27–0.88)			
Age	18–39	7 (20.6%)	27 (79.4%)	1	0.629		
	40–64	39 (15.2%)	218 (84.8%)	1.30 (0.45–3.72)			
	> 65	11 (16.7%)	55 (83.3%)	0.89 (0.43–1.86)			
Residency	Urban	46 (16.0%)	242 (84.0%)	1.00 (0.49–2.05)	0.995		
	Rural	11 (15.9%)	58 (84.1%)	1			
Educational status	Unable to read and write	18 (18.6%)	79 (81.4%)	1.02 (0.44–2.33)	0.972	0.75 (0.31–1.84)	0.530
	Elementary	21 (19.1%)	89 (80.9%)	1.05 (0.47–2.36)	0.904	0.85 (0.37–1.96)	0.698
	High school	7 (7.8%)	83 (92.2%)	0.38 (0.14–1.03)	0.058	0.29 (0.10–0.83)	0.021
	College and above	11 (18.3)	49 (81.7%)	1			
Physical exercise	Yes	20 (13.3%)	130 (86.7%)	1	0.249	0.77 (0.41–1.46)	0.430
	No	37 (17.9%)	170 (82.1%)	1.42 (0.78–2.55)			
History of other chronic illness	Yes	25 (16.0%)	131 (84.0%)	0.99 (0.56–1.76)	0.979		
	No	32 (15.9%)	169 (84.1%)	1			
Duration of DM	<6	41 (17.4%)	194 (82.6%)	1	0.291		
	≥6	16 (13.1%)	106 (86.9%)	1.40 (0.75–2.61)			
Duration of drug use	<6	41 (17.4%)	195 (82.6%)	1	0.312		
	≥6	16 (13.2%)	105 (86.8%)	1.38 (0.74–2.58)			
Blood pressure	Hypertensive	37 (17.1%)	179 (82.9%)	0.80 (0.44–1.44)	0.458		
	Normotensive	20 (14.2%)	121 (85.8%)	1			
BMI	Abnormal	33 (20.8%)	126 (79.2%)	0.53 (0.30–0.94)	0.028	1.94 (1.08–3.50)	0.027
	Normal	24 (12.1%)	174 (87.9%)	1			

due to variation in study design, sample size, and the reference range used for the CBC and coagulation tests. A comparative cross-sectional study conducted in a different part of the world also revealed that there is a shortening of PT and aPTT values among T2DM patients. This study finding is supported by different studies conducted by Ankalayya et al in India,<sup>45</sup> Mariappan et al in India,<sup>46</sup> Karim et al in Bangladesh,<sup>47</sup> Ephraim et al in Ghana,<sup>37</sup> Pan et al in China,<sup>48</sup> Sapkota et al in Nepal,<sup>49</sup> Asrat et al in Ethiopia,<sup>40</sup> and Ambelu et al in Ethiopia,<sup>24</sup> which showed that T2DM patients were presented with significant shortening of PT and aPTT.

In the present study, the prevalence of prolonged PT and aPTT results among T2DM patients were 5.6% (95% CI: 3.60, 8.40%) and 3.9% (95% CI: 2.30, 6.30%), respectively. The prevalence of prolonged PT is lower compared to Ebrahim et al study in Ethiopia that reported a 16.7% prevalence of prolonged PT among T2DM patients.<sup>44</sup> Nevertheless, the prevalence of prolonged aPTT is higher compared to Ebrahim's study that reported a 1.7% prevalence. The possible reason might be due to differences in sample size, reference range used, and the study design. A comparative cross-sectional study conducted by Alao et al in Nigeria,<sup>50</sup> Mohammed et al in Sudan,<sup>51</sup> Thukral et al in India,<sup>52</sup> and Ifeanyi et al in India<sup>53</sup> supported the presence of prolonged PT and aPTT results among T2DM patients.

Furthermore, the prevalence of thrombocytopenia among T2DM patients was 5.3% (95% CI: 3.30, 8.00%). Immune responses are thought to be responsible for the pathogenesis of thrombocytopenia in diabetic patients. An elevated level of platelet-associated Immunoglobulin G is observed among T2DM patients.<sup>54</sup> In this study, the prevalence of thrombocytopenia is in line with Ebrahim et al study in Ethiopia that reported a 5% prevalence.<sup>44</sup> In addition to this, studies that are conducted in different parts of the world supported the presence of thrombocytopenia among T2DM patients. A comparative cross-sectional study conducted by Pan et al in China,<sup>48</sup> Madan et al in India,<sup>55</sup> and Asrat et al in Ethiopia<sup>40</sup> showed that T2DM patients were presented with thrombocytopenia.



In addition to this, from the prolonged PT tests, coagulation factor deficiency and pathological factor inhibitors were observed among 95% and 5%, respectively. Whereas, out of the prolonged aPTT tests, coagulation factor deficiency and pathological factor inhibitors were observed among 92.8% and 7.14%, respectively. Pathological factor inhibitors are specific or non-specific inhibitors that halt normal coagulation cascade and result in delaying clot formation. Coagulation factor deficiency also results in a delay in the coagulation cascade.<sup>9,10</sup> Coagulation factor deficiency may be associated with the hypercoagulation condition in T2DM patients. The hypercoagulation may result in the consumption of one or more of the coagulation factors and it will cause factor deficiency.

In the current study, being female was significantly associated with hypercoagulation. Females were two times more likely to develop hypercoagulation than male patients. Hypercoagulation in female T2DM patients is associated with an increase in fibrinogen levels, FVII: C, Von Willebrand, and plasminogen activator inhibitor-1 than males.<sup>56,57</sup> This is in line with Chan et al in Taiwan<sup>13</sup> and Mwambungu et al in Zambia<sup>14</sup> studies that reported that female T2DM patients are at high risk of developing hypercoagulation. In addition, patients with abnormal BMI are also two times more likely to develop hypercoagulation than patients with normal BMI. Abnormal BMI, particularly in obesity, the risk of developing coagulation is high because adipocytokines increased activity of the coagulation factors, decreased activity of the fibrinolytic system, and endothelial dysfunction.<sup>58,59</sup> The educational status of High school also showed a significant association with hypercoagulation among T2DM patients. Study participants with educational status of high school are less likely to develop hypercoagulation. Study participants with educational status of high school were 71% less likely to develop hypercoagulation.

## Conclusion

The present study verified that the prevalence of coagulopathy among T2DM patients at the UoGCSH was a high public health problem. T2DM patients may experience numerous types of coagulopathies including hypercoagulation, a tendency to bleed, and abnormal platelet count. Moreover, factor inhibitors and factor deficiency were the cause for the coagulopathies observed among T2DM patients. Female T2DM patients and patients with abnormal BMI were two times more likely to develop hypercoagulation at the University of Gondar Comprehensive Specialized Hospital.

During a regular check-up of T2DM patients, coagulation parameters should be monitored at some time interval to diagnose coagulopathies. The hypercoagulation that is observed among T2DM patients is associated with abnormal BMI. Therefore, performing regular exercise is recommended to reduce the risk associated with it especially for female patients. In addition, for the coagulation factor deficiencies observed, a study that could assess specific coagulation factors can also be performed.

## Strengths and Limitations

The study's strength includes determination of the presence of factor deficiency and inhibitory through mixing test. Factors associated with coagulopathy were assessed in detail. The first major limitation of this study was being cross-sectional nature that does not reveal causal relations between independent variables and coagulopathy. Moreover, specific coagulation factor assays were not performed for the factor deficiencies determined.

## Abbreviations

AOR, adjusted odds ratio; aPTT, activated partial thromboplastin time; BMI, body mass index; CBC, complete blood count; COR, crude odds ratio; DM, diabetes mellitus; EDTA, ethylene diamine tetra acetic acid; GP, glycoprotein; IDF, International Diabetic Federation; NPP, normal pooled plasma; PPP, platelet poor plasma; PT, prothrombin time; T2DM, type II diabetes mellitus; UoGCSH, University of Gondar Comprehensive Specialized Hospital.

## Data Sharing Statement

All data supporting these findings is contained within the manuscript.

## Ethical Considerations

This study was conducted based on the Declaration of Helsinki. The study was conducted after ethical clearance was issued by the Ethical Review Committee of the School of Biomedical and Laboratory Sciences, College of Medicine and Health Science, the University of Gondar (Ref. No. SBLS/2746/2021). A permission letter was obtained from the UoGCSH. Informed written consents were obtained from each patient and the findings were kept confidentially. The confidentiality of the data was protected by only using codes for specimens and results and no personal identification was used. In case of abnormal results, it was informed to their medical doctors to get adequate treatment.

## Acknowledgments

First of all, we would like to thank the Department of Hematology and Immunohematology, the School of Biomedical and Laboratory Sciences, the University of Gondar. Next, we acknowledge the University of Gondar Comprehensive Specialized Hospital administrative office for their willingness during the data collection. Finally, we would like to extend our gratitude to the study participants for their voluntary and cooperative participation.

## Author Contributions

All authors participated in this study by conception of the study, data collection, feeding, performing the statistical analysis, drafting the manuscript, and read and edit the manuscript. All authors read and gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

## Funding

The authors received no specific funding for this work.

## Disclosure

The authors report no conflicts of interest for this work and declare that there is no conflict of interest regarding the publication of this manuscript.

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