A COMPARATIVE STUDY OF INR RATIO BETWEEN AUTOMATIC (ACL ELITE PRO) AND SEMIAUTOMATIC (ERBA) COAGULOMETERS

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List of abbreviations:

INR	International Normalized Ratio
PT	Prothrombin
PTT	Partial Thromboplastin Time
FBG	Fasting blood glucose
PS	Peripheral smear
OD	Optical Density
POC	Point-of-care
TEG	Thromboelastography
TTT	Tilt-Tube Technique
APTT	Activated Partial Thromboplastin Time
PNP	Platelets Neutralization Procedure
PAI	Plasminogen Activator Inhibitor
TAT	Thrombin /Anti Thrombin Complex
TF	Tissue Factor
ISI	International Sensitivity Index
WHO	World Health Organization
AVK	Anti-Vitamin K
IRP	International Reference Preparation
OTA	Oral Anticoagulant Therapy
MELD	Model for End Stage
VKA	Vitamin K Antagonists
PTR	Prothrombin Time Ration
SD	Standard Deviation

ABSTRACT

BACKGROUND

Hemostasis is a combination of many events that occur in a sequence following a breach of vascular integrity. It includes thrombus formation, vasoconstriction, platelet aggregation, recanalization, and healing. Secondary hemostasis is traditionally described as merging the intrinsic and extrinsic pathways at the common pathway.

The complex formed by the tissue factor VII and factor contributes to the activation of factor IX, demonstrating those intrinsic and extrinsic pathways almost from the beginning of the process. The process needs three consecutive phases: an initial phase, an amplification phase, and a propagation phase.

INR is the favourable test of choice for patients pre-operatively and also to assess the risk of bleeding or coagulation status. The INR is obtained from prothrombin time, calculated as a ratio of the patient's prothrombin time to control. Using the formula, PT standardized for the potency of the thromboplastin reagent developed by the World health organization is

INR = Patient PT / Control PT

Prothrombin time, the time in a sec is measured in plasma to form a clot in the presence of a significant concentration of calcium and tissue thromboplastin by activating coagulation via the extrinsic pathway.

OBJECTIVES OF THE STUDY

A COMPARATIVE STUDY OF INR VALUES BETWEEN AUTOMATIC (ACL

ELITE) AND SEMI-AUTOMATIC (ERBA) COAGULOMETERS.

MATERIALS AND METHODS

A Prospective study was conducted in the central laboratory, Pathology department, BLDE (Deemed to be University) Shri B. M. Patil Medical College, Hospital and Research Centre, Vijayapura, for testing of Prothrombin time, APTT and INR.

A total of 250 cases were studied. This study included Patients who came for measurement of PT, aPTT, and INR values. The values were measured using an automatic coagulometer (ACL PRO ELITE instrument, instrumentation laboratory company, Lexington, USA) according to the manufacturer's instructions and a Semi-automatic coagulometer(ERBA,

ECL 105, Transasia company, Germany) according to the manufacturer's instructions

RESULTS

This study included 250 patients who satisfied all the inclusion and exclusion criteria. One hundred and Thirty-four (54%) of the participants were male, and Sixteen (46%) were female, with a mean age of 37.66 ± 21 years.

The average Prothrombin total time obtained with the help of the ACL Elite Pro (Automatic) machine was around 14.51 ± 5.29 seconds, while the ERBA (Semiautomatic) machine was 13.5 ± 4.60 seconds.

The mean of Activated Partial Thromboplastin Time (APTT) obtained with the help of the ACL Elite Pro (Automatic) machine was 29.47 ± 8.30 seconds. In comparison, the ERBA (Semiautomatic) machine gave the value of 27 ± 6.96 seconds.

The ACL Elite Pro (Automatic) machine achieved the mean International Normalized Ratio (INR) of 1.22 ± 0.47 seconds, while the INR diagnosed with the help of the ERBA (Semiautomatic) machine was showed as 1.15 ± 0.46 seconds. The ACL Elite Pro and ERBA showed a statistically significant difference from each other ($p<0.05$).

CONCLUSION

The study showed good agreement between automated and semi-automated instruments based on mechanical end-point detection method and photo-optical end-point detection method for assessing coagulation tests, including PT, aPTT and INR values. Efficiency-wise, an automatic coagulometer (ACL COAGULOMETER) provides a slight edge over a semi-automated coagulometer (ERBA).

KEYWORDS

Coagulometer, semiautomatic, automatic, INR Value.

Graph-5:	Mean International Normalized Ratio (INR) value in ACL Elite Pro and ERBA.
Graph-6:	Correlation of INR value between Automatic and semiautomatic.

Introduction

Circulating blood performs many bodily functions, including transporting oxygen, carbon dioxide, and nutrients to every cell. Also, circulating blood is an excellent source of information on bleeding parameters, hypercoagulability, and fibrinolysis. Any injury or damage to the body acts as an instant stimulus for activation of blood coagulation cascades in which the conversion of blood fluid to surge to clumps of platelets occurs to prevent excess blood loss. Excessive blood coagulation, which causes hypercoagulability syndrome, results in blockages of major arteries and vessels due to excess clot formation that results in stroke, which can also be attributed to some other abnormalities of the blood and related coagulation process. [1,2]

Life-threatening diseases such as cancer [3], Human immunodeficiency virus infection (HIV) [4], hepatitis, trauma, [5] diabetes and retinal vein occlusion [6,7] cause severe complications and affect the coagulation stages.

Subtherapeutic anticoagulation is known to multiply the risk of clot formation, and thereby, stroke or venous thromboembolism is increased four folds in this process. In contrast, supratherapeutic anticoagulation is associated with an increased risk of bleeding. Therefore, it is essential to accurately measure and understand hemostasis to study defects in the sensing parameters of various disease models.[7]

This includes blood coagulation and fibrinolysis. Today, in the present era, when medical science is booming with all the technological advances, a growing coagulation test volume and budgetary constraints have increased the interest in automated coagulation analyzers. These instruments can be used, hemostatic defects can be detected, and anticoagulant therapy can be monitored through in vitro tests. However, in most of the tests, International Normalized Ratio (INR), Prothrombin

(PT) and Partial Thromboplastin Time (PTT) are based on the identification of a fibrin clot as the end-point. [8]

Table-1. Characteristics of INR, PT and aPTT

INR	**PT**	**aPTT**
The international normalised ratio (INR) is a measure of how long it takes blood to clot. The longer it takes blood to clot, the higher INR. INR is used to determine the dose of anticoagulants.	Prothrombin time (PT) is a blood test that measures the time it takes for the liquid portion (plasma) of blood to clot	A blood test that looks at how long it takes for blood to clot. It can help tell if there is a bleeding problem or if clotting occurs.

The international normalized ratio (INR) is the preferred preoperative test for patients to assess their risk of bleeding or coagulation status. The INR is obtained from prothrombin time, which is calculated as a ratio of the patient's prothrombin time to a control PT standardized for the potency of the thromboplastin reagent developed by the World Health Organization using the following formula: [9]

INR = Patient PT / Control PT

Prothrombin time, the time in seconds is measured in plasma to form a clot in the presence of a significant concentration of calcium and tissue thromboplastin by activating coagulation via the extrinsic pathway. The reference values of INR are

considered in prothrombin time measurement in device-related discrepancies, sensitivity, type of reagents used and differences in the tissue factor activator. The INR value ranges from 2.0 to 3.0. [9]

Comparison of the two coagulometers:

1. Semi-automatic **coagulometer (ERBA ECL 105, Transasia company, Germany):** which works on the principle of light scatter (640nm), clotting assays, and immunogenic turbidimetric assay (800nm) and gives the result of PT, aPTT, Fasting blood glucose (FBG) intrinsic and extrinsic factor assays, Peripheral smear (PS) and D-Dimer

2. Automatic coagulometer (ACL ELITE PRO):

In recent times, growing coagulation test volume and constricted personnel budgets have enhanced interest in automated coagulation analyzers.

There are two methods used for the detection of clot formation: Mechanical detection based on electromechanical and electromagnetic properties; and optical method based on photo-optical and photometric properties.

The plasma becomes turbid or opaque in automated and semi-automated optical instruments owing to fibrin formation. Two methods are used to detect clot formation: mechanical detection based on electromechanical and electromagnetic properties and an optical method based on photo-optical and photometric properties.

Electromechanical: A fibrin strand completing an electrical circuit forms the basis. A probe with two electrodes with current passing between them is dropped into a cup with plasma and reagents. The fibrin detected between the electrodes results in a detection circuit that senses the finished circuit, which is the end-point (fibrometer). [10]

Electromagnetic mechanical:

A rise in plasma viscosity when a fibrin form is the basis of the technique. A steel ball is oscillated within a cuvette under an electromagnetic field and monitored—clotting of the plasma sample slowdowns the ball movement, which forms the end-point. Interference by lipemia and bilirubinemia with the results attained using mechanical detection should not occur.[10]

Photo-optical:

Fibrin strand formation scatters the light that forms the basis. Clot formation in the plasma sample clots makes it optically denser and reduces the quantity of light falling on a photo-sensitive detector (i.e., transmitted light reduces). The reduction or alteration in light is considered the end-point. [11]

Photometric:

Occurrence of absorbency Optical Density (OD) of monochromatic light (uses filter) passing via the cuvette as the reaction being determined forms the basis. Measurement of transmitted light and conversion to absorbance determines the substance concentration. Lipemia, icterus, and hemolysis may interfere with the optical instruments. [12]

Many studies have been performed by using many high versions of the coagulometer. However, in resource-limited settings with feasible devices, there are not many studies. Hence, the present research was carried out to study the efficacy of our field's two most used coagulometers. The INR test is used to measure the time required for clot formation, which is also called prothrombin time (PT). This is used to monitor blood-thinning medicines. The INR value helps to check for any p roblems associated with blood clotting. This test helps to balance the risk of internal bleeding against the risk of blood clotting. [13]

In the last few years, the increasing demand for coagulation testing in laboratories has led to the development of a series of semi-automated or fully automated coagulometers. Generally, preference for one instrument over another has been given based on cost-effectiveness comparability, so the problems relating to comparability between instruments have been somehow neglected. [13] In principle, the difference in the results obtained with the different instruments should depend on both the detection system and the reagents adopted. The few published comparative studies have provided conflicting results, indicating a need for standardizing instruments and reagents. Automated coagulometers have improved coagulation testing efficiency in non-specialized laboratories.

Hence, the purpose of this present study was to compare the efficiency and reliability of two coagulometers in maintaining INR control of patients and their involvement in treatment. This study also helps emphasize the further practical use of instruments to improve patient adherence.

Need for the study:

Sub-therapeutic anticoagulation can multiply the risk of clot formation, thereby increasing the chance of stroke or venous thromboembolism, while supratherapeutic anticoagulation increases the risk of bleeding. Point-of-care (POC) International Normalized Ratio (INR) instruments using finger-stick whole blood samples are appropriate and preferred by patients due to the immediate results and less invasive means to acquire a blood sample. Point-of-care instruments are easy to use by either patients at home or health care professionals. The increased accessibility of Point care devices to measure the INR can improve the management of anticoagulation therapy; nevertheless, there have been many documented limitations regarding the accuracy and precision of these Point care instruments, especially INR measurements at the high-end of the INR range.

The present study helped compare the efficiency and reliability of two coagulometers in maintaining INR control of patients and involvement towards treatment. It also emphasizes the further practical use of instruments providing better patient adherence.

REVIEW OF LITERATURE

Historical background:

Medical professionals frequently measure blood levels and coagulation profiles as part of their clinical examinations. This type of clinical examination is an essential part of the test menu in modern medical laboratories. In this current era, routine coagulation testing is rarely performed via the time-honoured manual method. This procedure uses tilting test tubes, standard reagents, a stopwatch and large water tanks at 37°C. This traditional procedure is rarely used to reduce time and human error consumption. From ancient times, the manual tilt tube technique or mechanical hooking was used to measure coagulation time. [14]

Dedicated devices such as coagulation analyzers and coagulometers are now used in the medical field to perform coagulation tests. These instruments are of two types: semi-automated or fully automated coagulometers. [14]

According to the review article by **M. H. Qari** [14], The earliest coagulation method was described by **Huang Ti**, also known as the yellow emperor of China. He was the first to describe the length of time blood flows from the skin after it has been punctured, dating back to 3000 years ago. However, around 2,300 years ago, a crude assessment was also stated by hippo-crates. [14]

At around 16th century **Sydenham** gave information on bleeding time. Later on, during the 18th century, **Richardson** commented on the bleeding test, but it remained barely significant. After that, **Duke** in **1910** and **levy et al.** in **1935** came up with more sophisticated methods that were particular and standardized method and this method became a popular method for obtaining bleeding time.

In 1780, **Hewson** became the first who describe clotting time as the test. They noticed that the blood taken from the vein of a dog gets "jellied" in around 7 minutes. Before

the introduction of plasma clotting tests, this observation was interesting for many researchers. [15]

Many advances took place from 1822 to 1921. These included temperature control during clot formation, passing objects such as a fine needle through the blood to detect resistance, and using different sizes and shapes of glass tubes to view clot formation. In the early 1900s, researchers monitored the time it took whole blood to clot in a glass tube while it was tilted, a precursor to the Lee-White clotting time (1913). These early clotting time tests depended on observing the clot directly (visually) or microscopically.

Many advancements were made during the period 1822-1921. These numerous advances included temperature control during the clot formation, delicate objects were passed through the blood sample for the detection of resistance, and different capillary glass tubes (respective with their size and shape) were used to see the formation of the clot. Later, **Lee-White (1913)** reports that clotting time began as a precautionary measure in the early 1900s, as examiners tilted glass tubes to see how long it took for whole blood to clot. [14,15]

Kottman, in **1910 [16]**, was the first to report "Koaguloviskosimeter" as an instrument to detect clot formation. When blood gets clotted, the blood viscosity change can be measured using this instrument. During this process, a direct readout system measured an alteration in voltage. Voltage changes were plotted against time to measure clot formation.

After that, during the 1920s, plasma coagulation tests evolved. **Bender Gram** [17] added calcium chloride to anticoagulated blood plasma at 37° C in this test. They observed higher viscosity of the blood through fibrin monomer polymerization. The PT and PTT ratio estimation is based on principles used in thromboelastography (TEG) and sonar clot detection.

In these early days and for many years, the Coagulation test was initially performed in a 37° C water bath using plasma and reagents in a glass tube. The formation of the clot was determined by visual observation; for this examination, the stopwatch was used to determine the duration of time required for clot formation. This process or technique called as "Tilt-tube technique" (TTT).

Similarly, in late 1920, Nephelometers were the first instruments to measure clot formation. These instruments can measure the 90° light scattering of a colloidal suspension. The principle of this instrument is used to date. In these instruments, plasma clot formation observes as the change in light scatters with respect to time. [14]

The 1950s saw the development of the BBL Fibrometer, an instrument still found in coagulation laboratories, although it is no longer being manufactured. However, in the mid of 1950, the BBL fibrometer was still found in haematology laboratories. This instrument worked on the electromechanical clot detection method. This BBL Fibrometer instrument allowed pathological and haematological laboratories to move from manual tilt tubes and wire loops to a more accurate semi or fully-automated testing protocol.[14]

Consequently, in the early twentieth century, clot detector discovery included manual loops, a BBL Fibrometer or a rolling steel ball.

In many modern coagulation instruments, the principles of clot detection are similar to those used in these early analytical systems. A clot detection is either "observed" by an optical device (a nephelometric device) or "felt" by a mechanical device (a viscosity device). [18]

The new coagulation methodologies described below have further improved coagulation laboratory testing capabilities. Refinement of these methodologies has allowed the use of synthetic substrates and measurements of single proenzymes, enzymes, and monoclonal antibodies, which increases the ability to recognize the causes of disorders of hemostasis and thrombosis.

Assay end-point detection principle:

The available coagulometers are automated or semi-automated. Semi-automated coagulometers require the operator to manually deliver test plasma and reagents to the reaction cuvette and simultaneously limit testing to one or two specimens. These are relatively inexpensive instruments, but their use requires considerable operator expertise. [19]

Fully automated analyzers provide pipetting systems that automatically transfer reagents and test plasma to reaction vessels and measure the end-point without operator intervention. Multiple specimens can be tested simultaneously. [19] Automated coagulometers are expensive, and laboratory staff require specialized training to operate and maintain them. Regardless of technology, all semi-automated

and automated analyzers offer better coagulation testing accuracy and precision than manual methods. [19]

According to **Aller R (2003)**, [20] since 3000 years ago, the process of coagulation testing has significantly evolved seen first, in terms of refinement of the process itself and second, in automating these tests, a task that lasted over one century and resulted in the development of instruments that are capable of performing coagulation analysis accurately and precisely with a throughput of more than 550 tests per hour, when performing automated prothrombin time and activated partial thromboplastin time (APTT).

THE PRINCIPLE OF AUTOMATION:

The modern coagulometers consist of two most preferable modules. One is robotics, and the other is software. The communication between these modules enables us to perform numerous coagulation tests using the following principles, including clotting, chromogenic and immunological principles, as reported by **Kolde, H.J**.[21]

Table-2. Represents the examples of Various Analytical Methods Applied in Coagulation Testing [14, 21]

Clotting	Chromogenic	Immunulogical	Elisa
-P.T -aP.T.T -Thrombin time -Batroxin time -Mixing studies - Factor assays: II, VII, X, XI, XII, I, XIII, IX, VIII, II, V, VWBF, -Proteins C and S -F V leiden -Lupus anticoagulant screening, platelets neutralization procedure(PNP),Russel viper venom. -Reptilase time -Inhibitors assays -ristocetin cofactor assay	-A IIII - Activated Protein-C -Protein-S -Plasmin -Antiplasmin, tissue plasminogen activator t-PA,Urokinase -Heparine assay -F.assay:II, VIII, X, XIII -C1-inhibitor -Plasminogen activator inhibitor -Soluble fibrin monomers -Complement assay	-AT III -Protein-S -Protein-C -Platelet F4 -F-VII, IX, X. VWBF -D-Dimer - t-PA -Plasminogen activator inhibator (PAI)	-Thrombin/anti thrombin complex (TAT). -Prothrombin fragment F1 & F2

Table 2 represents the three testing principles that are the most widely used onboard modern coagulometers, allowing the user to carry out an extensive battery of coagulation assays simultaneously. The same assay can be performed in many instances using two different methods. Some of the assays carried out using more than one principle are illustrated in (Tab -1). [14]

Kerstin Göbel (2018)[22] reviewed the coagulation system. In this review, the author reported that the coagulation system is a tightly controlled cascade that, ultimately, results in the creation of blood clots. Hemostasis, or the cessation of bleeding from a damaged blood vessel, is the primary goal of coagulation.

In 1964, the idea of a sequential procedure or cascade of the coagulation system was first introduced by **Macfarlane RG.**[23]

The process of blood coagulation turns the circulating components of the blood into an intractable gel. The gel plugs seal blood artery leaks and stop blood loss. Coagulation factors, calcium, and phospholipids are necessary for the process.

- The liver develops the coagulation factors (proteins).
- Ionized calcium (Ca++) is available in the blood and from intracellular sources.
- Phospholipids are prominent mechanisms of cellular and platelet membranes. They provide a surface upon which the chemical reactions of coagulation can take place.

While the intrinsic and extrinsic pathways in this old model were defined as two distinct ways that met at a single pathway, contemporary theories support a related

relationship between these two pathways. [24, 25] These pathways are summarized as follows-

Intrinsic:

The Intrinsic pathway can be originated by events that occur inside the blood vessels' lumen. This pathway needs only elements (clotting factors, Ca++, platelet surface etc.) found inside the vascular system.[26]

Extrinsic:

The Extrinsic pathway is the other way of coagulation. It needs Tissue Factor (tissue thromboplastin), which is extrinsic to or not generally circulating in the vessel. The tissue factor is released when the vessel wall is ruptured. Irrespective of whether the extrinsic or Intrinsic pathway starts the coagulation process, completion of the process follows a general pathway. [26] Both pathways are essential for normal hemostasis, and positive feedback loops between the two pathways intensify the reaction to produce sufficient fibrin to form a lifesaving plug. Deficits or anomalies in any one factor can slow the overall process, increasing the risk of haemorrhage. The general pathway includes the activation of coagulation factors: X, V, II, XIII and I. In vitro, the initial triggering event induces the activation of Factor XII on a synthetic surface, which results in clot formation. [26]

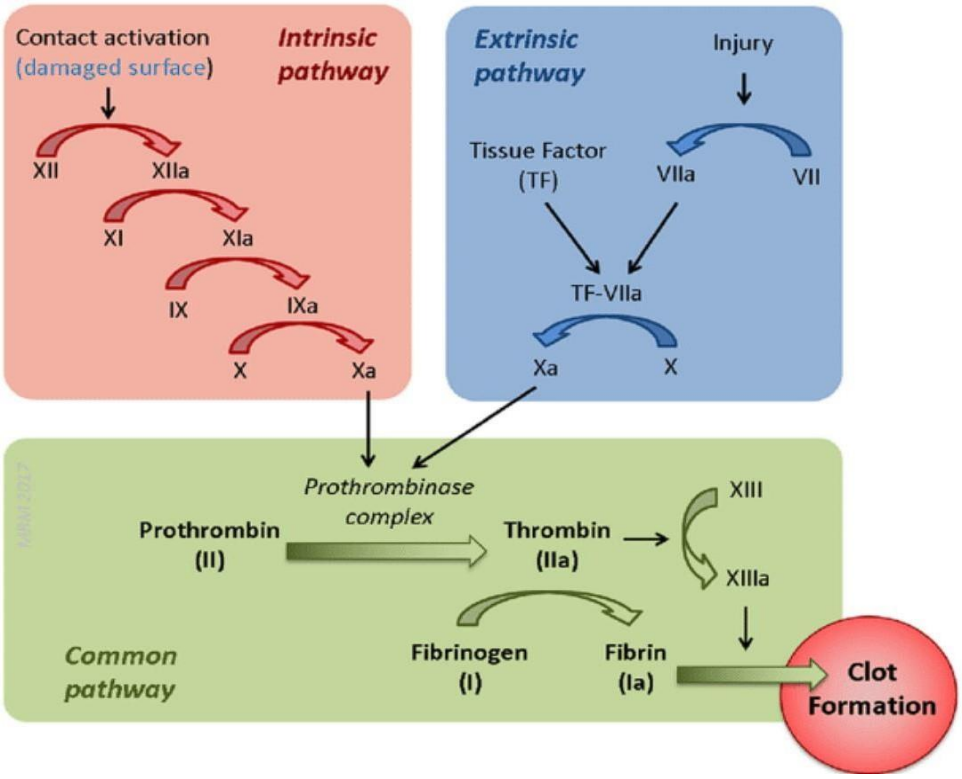


Figure-1

Current research considers tissue factor (TF), a transmembrane glycoprotein expressed in perivascular tissue, to be the primary initiator of in vivo blood clotting because the activation of this factor in vivo is still under debate. [27] To activate factor X (Factor-X), either directly or via activating factor IX, TF forms a complex with factor VII (Factor VII) (Factor IX). Prothrombin (Factor II) is split into thrombin by activating Factor X, which connects both routes (Factor IIa). [26] The final stage involves using thrombin to mediate the breakdown of fibrinogen into monomers of fibrin, which, when polymerized, form a fibrin clot and stop bleeding. The presence of thrombin, calcium and negatively charged phospholipid membranes is necessary for developing these clots. Numerous checkpoints that work in a positive or negative feedback loop strictly govern the entire coagulation cascade.[28]

The numbered of coagulation factors represented the order of their discovery. There are a total of 13 numerals but only 12 factors. Factor VI was later found to be part of another factor. The following are coagulation factors and their common names. [26]

Table-3. Representing all coagulating factors in biological system.

1	Factor I	fibrinogen
2	Factor II	prothrombin
3	Factor III	tissue thromboplastin (tissue factor)
4	Factor IV	ionized calcium (Ca++)
5	Factor V	labile factor or proaccelerin
6	Factor VI	unassigned
7	Factor VII	stable factor of proconvertin
8	Factor VIII	antihemophilic factor
9	Factor IX	plasma thromboplastin component, Christmas factor
10	Factor X	Stuart- prower factor
11	Factor XI	plasma thromboplastin antecedent
12	Factor XII	Hageman factor
13	Factor XIII	fibrin-stabilizing factor

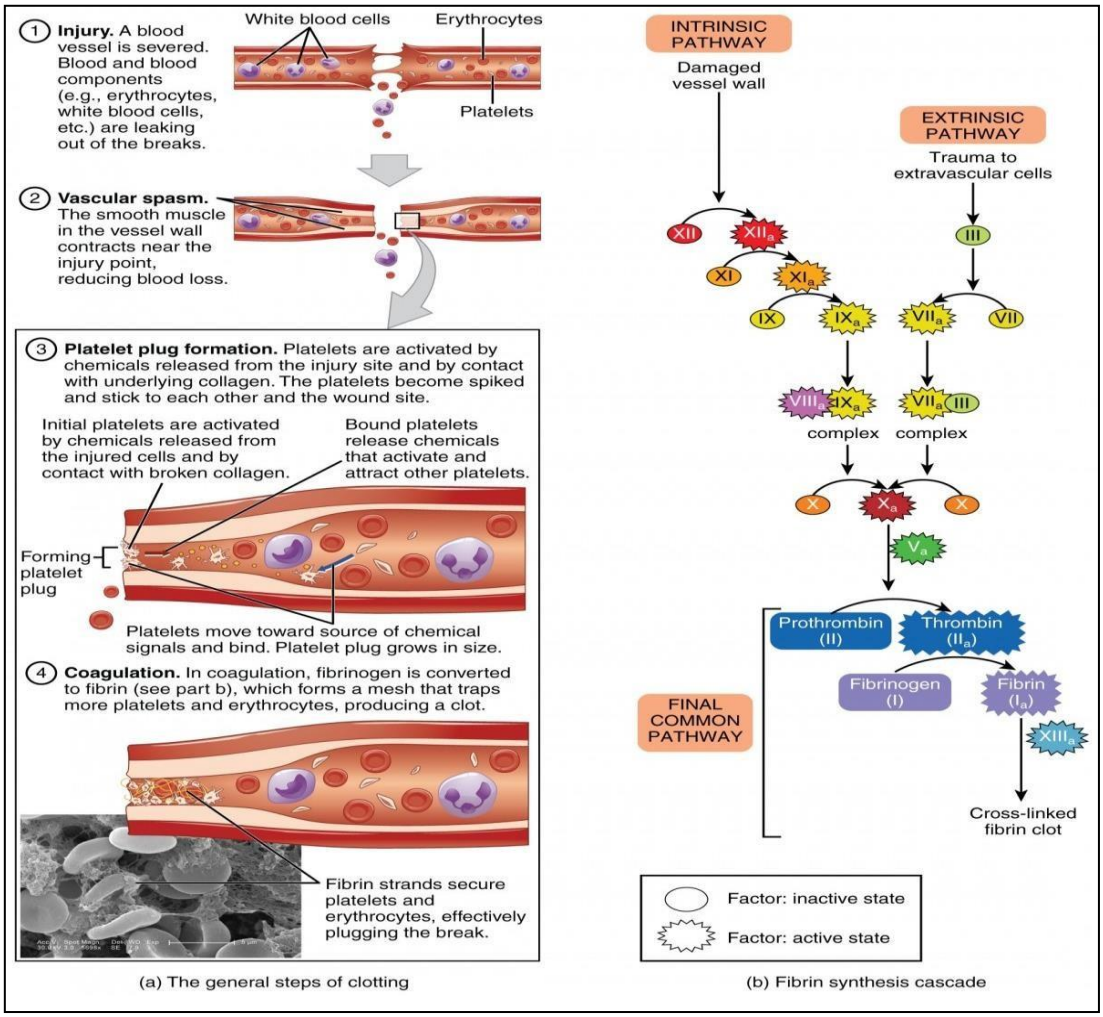


Figure-2: Intrinsic and Extrinsic pathway and clotting factors.

Coagulometer:

An instrument known as a blood coagulometer is used to test the blood's ability to clot to diagnose and evaluate bleeding diseases like haemophilia or to keep track of patients taking anticoagulant drugs like aspirin, heparin, or warfarin.

Prothrombin time (PT):

The prothrombin time (PT) signifies the greatest generally used coagulation test in clinical laboratories. Normal blood plasma in the PT clots around within 10 to 12 seconds, which triggers the coagulation process, and the normal reference range is generally narrow. [29]

The prothrombin time (PT) represents the greatest generally used co-angulation test and was first announced in use by Dr Armand Quick and colleagues (1935). [30] In order to provide test results that are corrected for thromboplastin and the instrument used, the PT is mathematically converted to the international normalized ratio (INR) for use in monitoring anticoagulant therapy with vitamin K antagonists like (**Wisconsin Alumni Research Foundation)** warfarin. [29]

The activity of coagulation factor II (Factor II), V (Factor V), VII (Factor VII), X (Factor X), and fibrinogen has an impact on the PT since it is a single-stage screening test used to assess the tissue factor (TF) and common coagulation pathways. [31]

aPTT:

The activated partial thromboplastin time is a clot-based test of the intrinsic and common coagulation pathways. It is typically used to monitor the usage of unfractionated heparin and screen for inherited and acquired coagulation abnormalities. It was developed as PTT in 1953 by Langdell et al. [32], in which the phospholipid and calcium chloride stimulated the coagulation. [32]

In 1961, Proctor and Rappaport used kaolin to activate the contact factors to show the (APTT) change. In contrast to thromboplastin, a compound of tissue factor and phospholipid, the test's name comes from a partial thromboplastin or procoagulant phospholipid that initiates the clotting mechanism. The coagulation system is made up of co-factors, cations, and cell-associated phospholipids, as well as proenzymes that are often inactivated in the intravascular environment. [10]

The coagulation is triggered by the two main processes, intrinsic and extrinsic routes, which combine to produce thrombin via a shared pathway of several related enzyme events. [33] There are two stages to performing the aPTT. In the first stage, the aPTT reagent includes a standardized amount of procoagulant phospholipids, interacts with the activator, and is added to the citrated anticoagulated plasma. Later after standard incubation time, calcium chloride is added then the clotting time is measured. The activator varies but is commonly kaolin, silica, ellagic acid, or another negatively charged substance. [34]

Based on the International Sensitivity Index (ISI) of thromboplastin substances to deliver International Normalized Ratios (INR), the World Health Organization (WHO) recognized an arrangement for prothrombin time (PT) standardization over 20 years ago. [35]

INR:

In 1983, Kirkwood established the international normalized ratio system, which was proposed to complement the results among the different substances. For most Anti-Vitamin K (AVK) treatment suggestions, the therapeutic range is optimal if INR

values fall between 2.0 and 3.0. 1. [36] Therefore, it is clear that for the period of therapy, often a lifetime, and patients must undergo these periodic checks. Ideally, every 3–4 weeks or less, this duration and the World Health Organization (WHO) arrangement for prothrombin time regularization based on international normalized ratios (INRs) was established more than 25 years ago. [36] With this program, INRs result from manual PT, using the pertinent WHO human, rabbit, or bovine species international reference preparation (IRP) for thromboplastin. Moreover, manual testing has been changed nearly universally and replaced by computerized testing techniques, making the WHO suggest ISI. The World Health Organization scheme for prothrombin time regularization based on INRs was established more than 25 years ago [37]with this program, INRs result from manual PT trying using the pertinent WHO human, rabbit or bovine species international reference preparation (IRP) for thromboplastin. Moreover, computerized techniques have transformed manual testing nearly universally, making the WHO-suggested ISI more critical. In addition, INR monitors oral anticoagulant therapy to reduce the risk of thromboembolic events and minimize the incidence of bleeding complications. [37] This improved the safety and effectiveness of oral anticoagulant treatment by providing INR every day for reporting different PT procedures. Correct INR is essential for the safety and effectiveness of oral anticoagulant treatment. Below an INR of 2.0 and above an INR of 4.5, the incidences of thrombotic and bleeding events increase exponentially. [38, 39]

Some published literature on INR ratio:

A study done by **Giddings JC et al. (1989)[40]** stated that clinical investigation might be affected by automated blood coagulation instruments. According to the study, the PT test using automatic coagulometers may not show results the same as the manual

method and alteration in the outcome of results may be critical for clinical investigation. The Institute of Medical Laboratory Sciences advisory committee suggested using coagulometers to determine prothrombin times only if the results are comparable with those obtained by standardized manual methods.

Vacas M et al. (2001). [41] investigated a comparative study on the CoaguCheck coagulometer and three routine methods, including capillary, plasma and whole blood samples used to monitor PT and correlate capillary blood results. Two hundred thirty-five participants were included in this study from three different tertiary care hospitals, and all underwent participants treated with oral anticoagulant therapy (OTA). The INR ratio obtained from the CoaguChek instrument was compared with routine methods. The results of this study present a good correlation between PT monitoring and the routine, as mentioned earlier, three methods. The mean and SD values were noted in laboratory (A), and CoaguChek INRs were approximately 0.0571 ± 0.2042. In contrast, laboratory (B), values were found to be around 0.04286 ± 0.3906, and in laboratory (C), the mean and SD were showing 0.6986 ± 0.6170. Thereby results confirm that CoaguChek could be used as a new method for OAT investigation, and it is in good agreement with the capillary blood PT system.

A case report by **Kakkar N and Garg G (2005)**[42] showed that coagulometers are in high demand worldwide. The accuracy and ability of coagulation tests have improved over the last few decades. It is important to note that, even with sophisticated coagulometers, test results of these coagulometers can be subject to errors because of both analytical and pre-analytical factors. Results of this study report turbidity in the test plasma can cause erroneous outcomes from coagulometers using absorbance variation for end-point detection.

Belle L et al. (2007). [43] reported that 60 patients were admitted who were critically ill with chronic or acute liver failure.

Patients were enrolled based on their PT reports as a ratio of thromboplastin of the laboratory range of PT in liver failure. In this study, the author stated that the INR "LD" might provide a general worldwide score of PT reporting in the hepatology department. Its adoption would be a significant step due to its remarkable impact on the Model for End Stage (MELD) score encouraged by interlaboratory variability in INR determination.

According to the study done by **Shetty et al. (2008)**[44] Semi-automated coagulometer used in this study, four reagents were used, including Platelin LS; Silimat; Actin FSL; and CK Prest were tested against Seventy-five plasma samples, these samples were collected from average individual or who were with haemostatic complications. In mild factor VIII and factor IX deficiency, different aPTT reagents missed different proportions (36.4, 18.2, 4.6, and 13.6%, respectively). In comparison, abnormal results were observed with normal plasmas (more than 5s prolongation) (reagents 29.2%, 25, 8.3, and 12.5%, respectively). At the same time, some reagents produce a falsely prolonged aPTT with normal plasma in mild cases of factor VIII and factor IX deficiencies.

Another study was conducted by **Hur M et al. (2013)** [45]**,** who investigated 118 cases. The author and their co-workers used CoaguChek XS (automatic) plus and STA-R (semi-automatic) coagulometer in this study. Statistical analysis was performed using Passing/Bablok regression and the Bland-Altman plot. This study showed a strong correlation (0.964) of INR measurements was excellent when compared between CoaguChek XS Plus and STA-R. INR results increased with time

and were 0.25. There was a difference in dose decision in 21/118 (17.8%) of INR measurements (kappa = 0.679). Hence, the author suggested CoaguChek XS Plus is a reliable tool and very efficient compared to the STA-R coagulation analyzer.

Similarly, in **2008**, a study by **Karon BS et al.** [46] stated the various manageable coagulometers developed to evaluate the INR ratio. In haematology, using POC devices has reduced the need to separate blood plasma with the help of the centrifugation technique; hence, advanced instruments evolved in the current era make VKA monitoring easier.

Sobieraj-Teague M et al. (2009). [47] report the clinical usefulness of CoaguChek S and XS monitors to measure INR when warfarin preliminary started in community patients. In this study, the author observed when preliminary warfarin started, the prevalence of CoaguChek XS was the choice for outpatient INR monitoring.

According to a study published by **Donaldson M et al**. [48] in **2010,** reported 52 patients got oral warfarin treatment. These patients had their INR values, which were measured using two devices. One was automatic, i.e., CoaguChek XS Plus, and the other was i-STAT PT/INR. Similarly, the reference laboratory's devices collected the venous blood sample from every patient at the same visit for INR evaluation. The absolute difference for each set of INR ranges was calculated to measure accuracy. Based on the findings of this study, a comparison of STAGO and CoaguChek XS Plus measured INR within 0.001 was obtained by comparing the absolute differences of 0.28 ± 0.31 (mean + SD). The absolute difference in INR ratio calculated by using both devices was 0.51 ± 0.44 ($p < 0.0001$). Compared with laboratory-based

venipuncture, measurements of INR produced by POC devices revealed a positive bias for high INR values.

In **2015,** a prospective study by **M Meneghelo et al.** [49] showed 1009 cases using Vitamin K antagonists (VKA) in the anticoagulation clinic at the Institute Dante Pazzanese of Cardiology in Sao Paulo from July 2012 to September 2012. Among the selected patients, INR values were obtained with the laboratory investigation via venipuncture. Then, it was compared to INR values obtained with the help of capillary puncture from 2 different coagulometers. Results of this study showed common indications such as atrial fibrillation and mechanical prosthesis in which 49.9% and 33.7% of patients were seen. Whereas of the 1009 patients, 520 were male with an average mean age of 59.6 years. When INR ration PT @Monitor and compared to laboratory investigation, they found 0.95 was the correlation coefficient and 0.88 with INR ration PT @Monitor. In patients with an INR below 2 (below the therapeutic range), CoaguChek XS plus (®) and INRatio PT Monitor(®) showed coefficients of 0.92 and 0.81, respectively. In cases within a therapeutic range between INR 2-3, the coefficient was noted as 0.86 with CoaguChekXSPlus (®) and 0.76 with INRatio PT Monitor®. For INR above the therapeutic range (INR > 3.0), the correlation was 0.80 with CoaguChek XS Plus (®) and 0.54 with INRatio PT Monitor (®). The author concludes that a portable coagulometer is a convenient and reliable tool for INR control in cases using Vitamin K antagonists. The machines in comparison were CoaguChek XS plus (Portable coagulometer) and INR ratio Prothrombin time Monitor (Laboratory coagulometer).

Baker WS et al. (2017). [50] conducted a study on 100 warfarin therapy patients and 20 coagulation normal subjects using CoaguChek XS (Automatic) and on-site STA-GO analyzers (Semi-Automatic). The CoaguChek XS and on-site STAGO analyzers show reasonable agreement for INR <3.0 but a significant difference for INR ≥ 3.0.

Kalçık M et al (2017). [51] compared the INR results achieved by a portable coagulometer and an std. Laboratory method with the help of (CoaguChek XS) and (STAGO STA-R) coagulometer. In this study, a total of 433 patients participated. Among these, 191 were male, and the rest patients were female with a median age of 61 [44-86] years who underwent the anticoagulation clinic. CoaguChek XS portable coagulometers and STAGO STA-R automatic laboratory coagulometers were used to measure INR in each patient. The Pearson correlation test and Cohen K test evaluated the association between these methods. In this study, the author concluded that a rapid and reliable INR test is provided by the CoaguChek XS coagulometer, which was found to be very consistent with traditional laboratory testing.

Another study was done by **Moiz B et al. (2018)** [52] **at** Aga Khan University Hospital, Pakistan, from July 2013 to March 2014. A total of 100 individuals were considered as a sample size. The coagulometers compared were the POCT coagulometer (CoaguChek XS Pro) and laboratory analyzer (Sysmex CS2000i). The comprehensive correlation of the INR measurements between the two methods was excellent without significant deviation from linearity.

Kaur M et al. (2018). [53] showed the comparison between the std. Tilt method and semi-automated coagulometer for the estimation of PT and INR. This research was performed in the Haematology Department for one year, in which 400 anticoagulated

blood specimens were selected. The std. manual tilt method and semi-automated coagulometer were applied to estimate PT from all included specimens. Estimated PT values were altered to Prothrombin Time Ration (PTR) and INR. The findings of this study showed a high degree of concordance for PT, PTR and INR evaluated by manual and automated methods. However, the intra-method precision was found to increase with the automated method. The risk of bias and 95% CI were higher in the manual method than in the automated method.

Moreover, statistical analysis showed non-significant differences in both methods. The author and their co-worker observed that manual and automated methods show good concordance. However, for higher sample throughput in everyday laboratory day-to-day practice, numerous management may not be reproducible consistently due to inter-observer differences brought about by numerous management.

Overview of advantages of semi and auto- coagulometer: [54]

1. Improves the capacity and flexibility of time spent by a professional.
2. Improves test reproducibility.
3. Reduces costs in samples and reagents.
4. Facilitates data storage and recovery systems utilizing computer programmes.
5. Provides automatic replay of results when mistakes are made in the first run.
6. Allows different tests to be run simultaneously using a single sample.
7. Permits sampling from a closed tube, which improves safety and efficiency in coagulation tests.
8. Enables analyzers to dilute samples, calibrators and controls.

AIM AND OBSERVATION

Aim: To study the comparison of INR ratio between automatic (ACL ELITE PRO) and Semi-automatic (ERBA) coagulometers.

Objectives of the study:

· A comparative study of INR values between automatic (ACL ELITE PRO) and semi-automatic (ERBA) coagulometers.

· To calculate the correlation between PT and INR in an automatic (ACL ELITE PRO) coagulometer

· To calculate the correlation between PT and INR in a semi-automatic (ERBA) coagulometer

MATERIALS AND METHODS:

A. Study design:

The current study was a prospective study. The purpose of the study was to compare the efficiency and reliability of two coagulometers in maintaining INR control of patients and their involvement in treatment. It also emphasizes the further practical use of instruments to improve patient adherence.

B. Study Area:

This study was conducted in the Department of Pathology at BLDE (Deemed to be University) Shri B.M. Patil Medical College, Hospital and Research Center, Vijayapura. Ethical approval was taken from the Institutional Ethics Committee to conduct this study.

C. Study period:

Duration of the study from January 2021 to July 2022.

D. Study Population:

The blood samples were collected randomly from 250 patients by a standard venipuncture technique under aseptic conditions.

Inclusion criteria

• Patients who are on drugs like chlorpromazine, heparin, and salicylates.

• Patient who has liver disease.

Exclusion criteria:

• PT, APTT Values above 100 as automated coagulometer shows error.

Financial disclosure:

The institution does not fund this study.

Methods of collection of data:

In this present study, patients who came for measurement of PT, aPTT, and INR values were included. These values were measured using an automatic coagulometer (ACLPRO ELITE instrument, instrumentation laboratory company, Lexington, USA)

and a semi-automatic coagulometer (ERBA ECL 105, Transasia company, Germany) according to the manufacturer's instructions.

Sample size:

The expected mean SD of INR values among patients tested with automatic and semi-automatic coagulometers was 2.54±1.17, and 2.79±1.39 respectively (ref), and a minimum sample size of 250 was required to achieve a power of 80% and a level of significance of 5% (two-sided) for detecting an actual difference in means between the testing groups.

The formula used:

$N=2Za+z\beta*Sd2$

Za Level of significance=95%

Zβ--the power of the study=90%

d=clinically significant difference between two parameters

SD= Common standard deviation

Data collection technique and tools:

All samples were analyzed for PT, INR, and aPTT within two hours of sample collection on the (ACLPRO ELITE instrument, instrumentation laboratory company, Lexington USA) automated coagulation analyzer using the photo-optical clot detection method and semi-automatic (ERBA ECL 105, Transasia company, Germany) Coagulometers.

We used a single assay kit batch for all analyses to minimize analytical performance variability. The within and between-batch imprecision was consistent with the manufacturer's product information. Hemos ® was used for the determination of thrombin time in vitro diagnosis. For the measurement of PT (International Sensitivity Index: 1.04) reagent was used. Similarly, APTT was measured by using Calcium chlorideTMstandardized at -0.025 mol/l concentration reagent. The blood samples received in the laboratory were centrifuged for 5 minutes in a tabletop centrifuge to obtain platelet-poor plasma (PPP). PT, INR, and aPTT were run on the PPP, and the results obtained were taken as baseline values (zero hours). The rest of the PPP was aliquoted and stored in microcentrifuge tubes (MCT), three each in the freezer, in the refrigerator, and at room temperature to be analyzed at 12 h, 24 h and 36 h. The analysis was completed within two hours on the automated coagulation analyzer. All the results were categorized into two groups. The average coagulation profile was defined as a PT between 9.9 and 13.5 seconds, an INR between 0.83 and 1.25, and an APTT between 21.7 and 29.3 seconds. The deranged coagulation profile was defined as PT>13.5 seconds, INR >1.25, and APTT>29.3 seconds.

Statistical Analysis:

· The data obtained were entered into a Microsoft Excel sheet, and statistical analysis was accomplished using a statistical package for the social sciences (Version 20).

· Results were presented as Mean ± SD, counts and percentages, and diagrams.

· For normally distributed continuous variables among two groups were compared using an Independent t-test for not normally distributed variables, the Mann Whitney U test was used. Categorical variables between the two groups were compared using the Chi-square test.

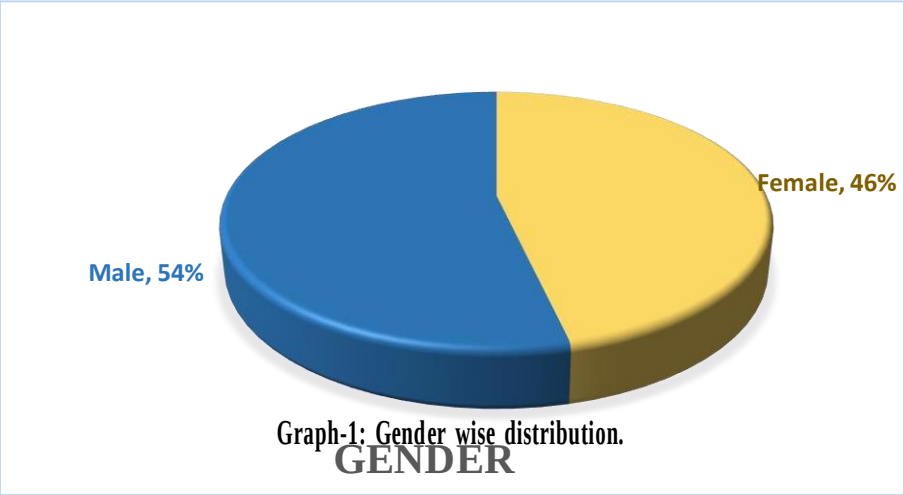
· Correlation between the variables was analyzed using Pearson's/Spearman's correlation coefficient.

· $p<0.05$ was considered statistically significant. All statistical tests were performed in two-tailed.

OBSERVATIONS AND RESULTS

This prospective study was conducted on "Comparative study of INR ratio between automatic and semi-automatic coagulometers" in the Department of Pathology at Shri. B.M. Patil Medical College, Hospital and Research Centre, Vijayapura, from January 2021 to July 2022. In this study, 250 patients who satisfied all the inclusion and exclusion criteria were included. One hundred and Thirty-four (54%) of the participants were male, and One hundred and Sixteen (46%) were female, with a mean age of 37.66 ± 21 years, as illustrated in **Table 4** and **Graph 1**.

Gender	No. of cases	Percentage
Female	116	46%
Male	134	54%
Total	250	100%



Graph-1: Gender wise distribution.

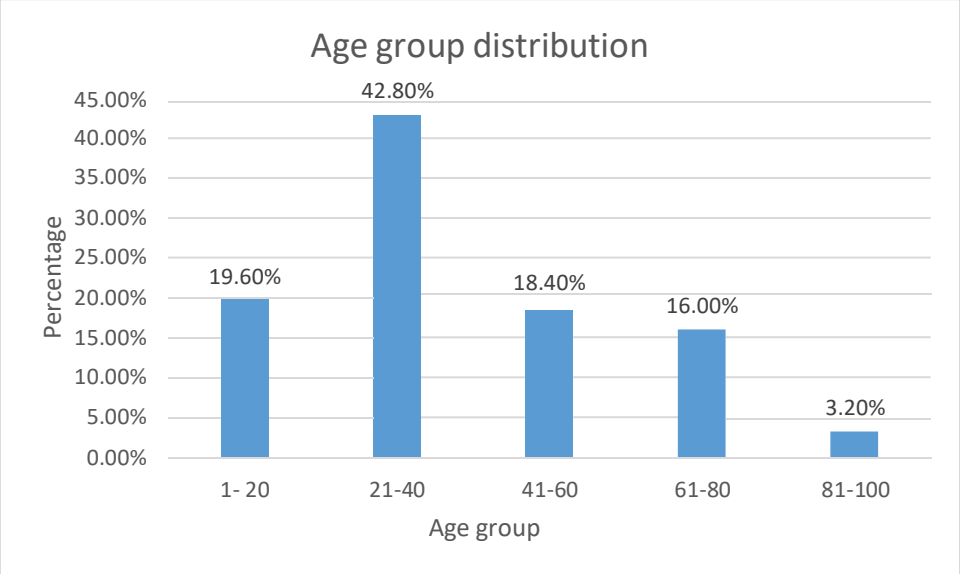
Table-4: Gender wise distribution of patients.

Majority of patients were between the age of 21 to 40 (n=107) 42.80% while only (n=8) 3.20% were over the age of 80 to 100, (n=40) 16% were between 61 to 80 years, (n=46) 18.40% patients were between the age of 41 to 60 years and (n=49) 19.60% patients were between the age of 1-20 years. **(Table-5/Graph-2)**

Table-5: Distribution of patients according to age group.

Age group (In Years)	No. of cases	Percentage (%)
1- 20	49	19.60%
21-40	107	42.80%
41-60	46	18.40%
61-80	40	16.00%
81-100	8	3.20%

Graph- 2: Distribution of patients according to age group.



In our series, the maximum number of patients were between 21-40 years, in which case (n=61) 26.40% were female and (n=41) 16.40% were male. Whereas in the age group of 41-60 years (n=34), 13.60% were male and (n=12) 4.80% were female, while in the age group of 61-80 years, there were (n=27), 10.80% were male and (n=13) were female. Similarly, a minority of patients were between the age of 81-100

years, i.e., (n=6) 2.40% were male, and only (n=2) 0.80% were female. There were the most cases (n = 26) in the paediatric to adolescent age range, around 1-20 years of age. 10.40% were male, and (n=23) 9.20% were female **(Table 6).**

Table-6. Distribution of patients according to age groups and gender.

Age group (In Years)	Gender	No. of cases	Percentage
1- 20 Yrs	Male	26	10.40%
	Female	23	9.20%
21-40 Yrs	Male	41	16.40%
	Female	66	26.40%
41-60 Yrs	Male	34	13.60%
	Female	12	4.80%
61-80 Yrs	Male	27	10.80%
	Female	13	5.20%
81-100 Yrs	Male	6	2.40%
	Female	2	0.80%

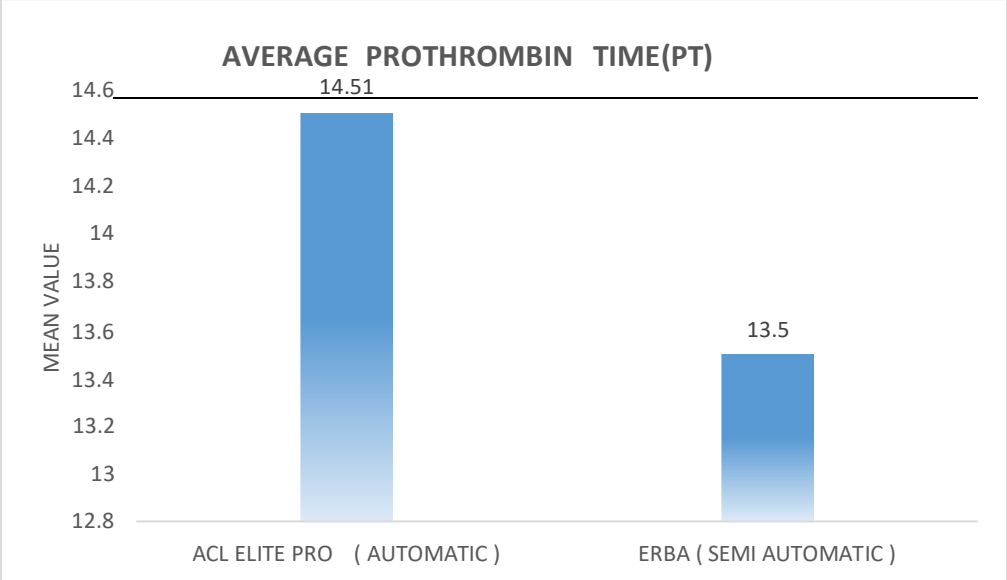
According to **Table-7** and **Graph-3**, the average Prothrombin total time diagnosed with the help of the ACL Elite Pro (Automatic) machine was around 14.51 ± 5.29 seconds, while the ERBA (Semiautomatic) machine was 13.5 ± 4.60 seconds for prothrombin time. A statistically significant difference between the two machines was discovered between the ACL Elite Pro and ERBA ($p<0.05$).

Table-7: Mean Prothrombin time between Automatic and Semi-Automatic

Prothrombin Time (PT)	Mean ± SD	P-value
ACL ELITE PRO (AUTOMATIC)	14.51 ± 5.29	p<0.05
ERBA (SEMI AUTOMATIC)	13.5 ± 4.60	

P<0.05= Significant

Graph-3: Average Prothrombin time.



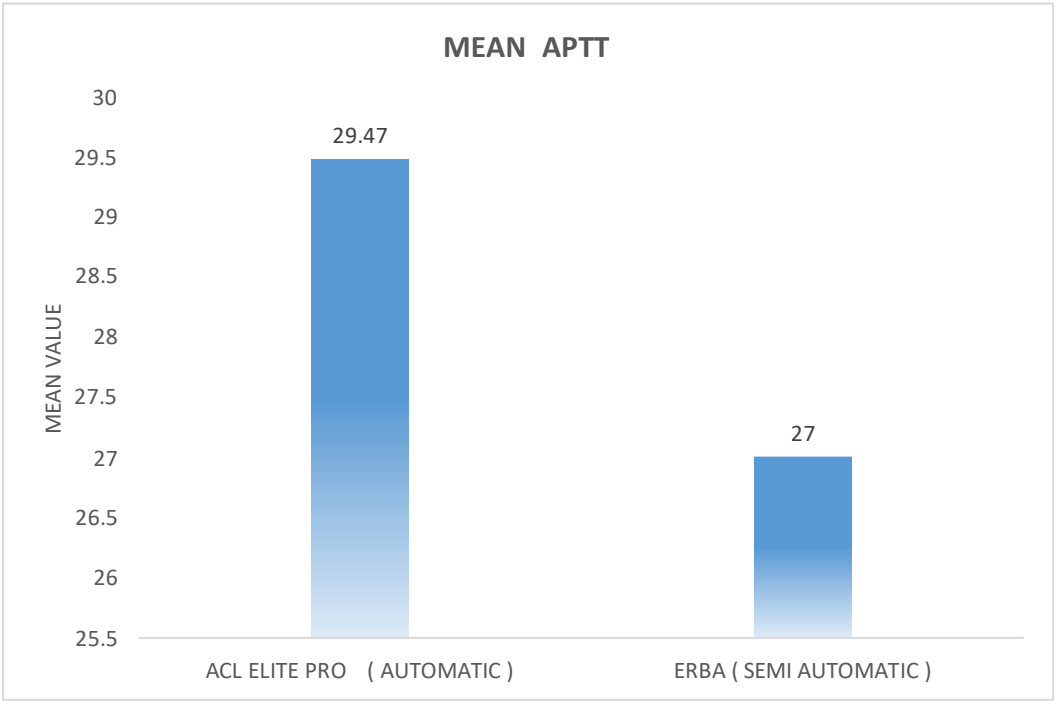
According to **Table-8/ Graph-4**, the mean of Activated Partial Thromboplastin Time (APTT) diagnosed by the ACL Elite Pro (Automatic) machine was 29.47 ± 8.30 seconds. The ERBA (Semiautomatic) machine required 27 ± 6.96 seconds to diagnose APTT. A statistically significant difference between the two machines was discovered between the ACL Elite Pro and ERBA (p<0.05).

Table-8: Mean value of aPTT and p-value in ACL Elite Pro (Automatic) and ERBA (Semi-automatic).

Activated Partial Thromboplastin Time (APTT)	Mean ± SD	P-value
ACL ELITE PRO (AUTOMATIC)	29.47 ± 8.30	p<0.05
ERBA (SEMI AUTOMATIC)	27 ± 6.96	

P<0.05= Significant

Graph-4: Mean aPTT value in ACL Elite Pro and ERBA.



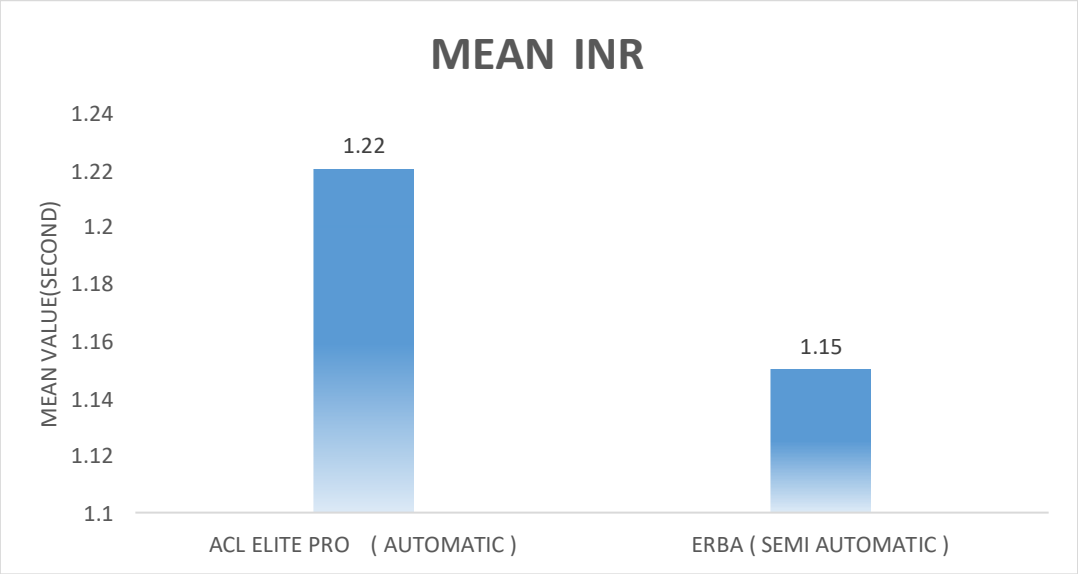
In the present study, the following **Table-9** and **Graph-5** showed that the ACL Elite Pro (Automatic) machine achieved the mean International Normalized Ratio (INR) was 1.22 ± 0.47 seconds while the INR diagnosed with the help of the ERBA

(Semiautomatic) machine was showed 1.15 ± 0.46 seconds. The ACL Elite Pro and ERBA were shown to have a statistically significant difference from each other ($p<0.05$).

Table-9: Mean value of INR and p-value in ACL Elite Pro (Automatic) and ERBA (Semi-automatic).

International Normalized Ratio (INR)	Mean ± SD (in Second)	P-value
ACL ELITE PRO (AUTOMATIC)	1.22 ± 0.47	p<0.05
ERBA (SEMI AUTOMATIC)	1.15 ± 0.46	

Graph-5: Mean International Normalized Ratio (INR) value in ACL Elite Pro and ERBA.



In the present investigation, we found a positive correlation between PT and INR in automatic machines with 0.95. If the value of Prothrombin Time (PT) increases simultaneously, INR also increases **(Table 10).**

Table-10: Correlation coefficient between PT and INR (Automatic) – Correlations

			PT	INR
Spearman's rho	PT	Correlation Coefficient	1.000	.952**
		Sig. (2-tailed)	.	.000
		N	250	250
	INR	Correlation Coefficient	.952**	1.000
		Sig. (2-tailed)	.000	.
		N	250	250

**. Correlation is significant at the 0.01 level (2-tailed).

Our findings show aPTT and INR had been noted with a weak positive association, around 0.31. This implies that if the Activated Partial Thromboplastin Time (aPTT) increases, INR values increase, as shown in **Table 11**.

Table-11: Correlation coefficient between aPTT and INR (Automatic) correlations

			ATPP	INR
Spearman's rho	ATPP	Correlation Coefficient	1.000	**.314****
		Sig. (2-tailed)	.	.000
		N	250	250

	INR	Correlation Coefficient	**.314****	1.000
		Sig. (2-tailed)	.000	.
		N	250	250

**. Correlation is significant at the 0.01 level (2-tailed).

According to following **Table 12** shows there was a strong positive correlation between PT and INR in the semi-automatic machine. Based on the present findings, we suggest that the INR value increased due to increasing Prothrombin Time.

Table-12: Correlation coefficient between PT and INR (Semi-automatic)

correlations

Correlations

			PT	INR
Spearman's rho	PT	Correlation Coefficient	1.000	**.976****
		Sig. (2-tailed)	.	.000
		N	250	250
	INR	Correlation Coefficient	**.976****	1.000
		Sig. (2-tailed)	.000	.
		N	250	250

**. Correlation is significant at the 0.01 level (2-tailed).

In the present investigation, we found a strong positive relation between ATPP and INR among semi-automatic machines. This shows that INR values increase with respect to the Prothrombin time. **(Table-13)**

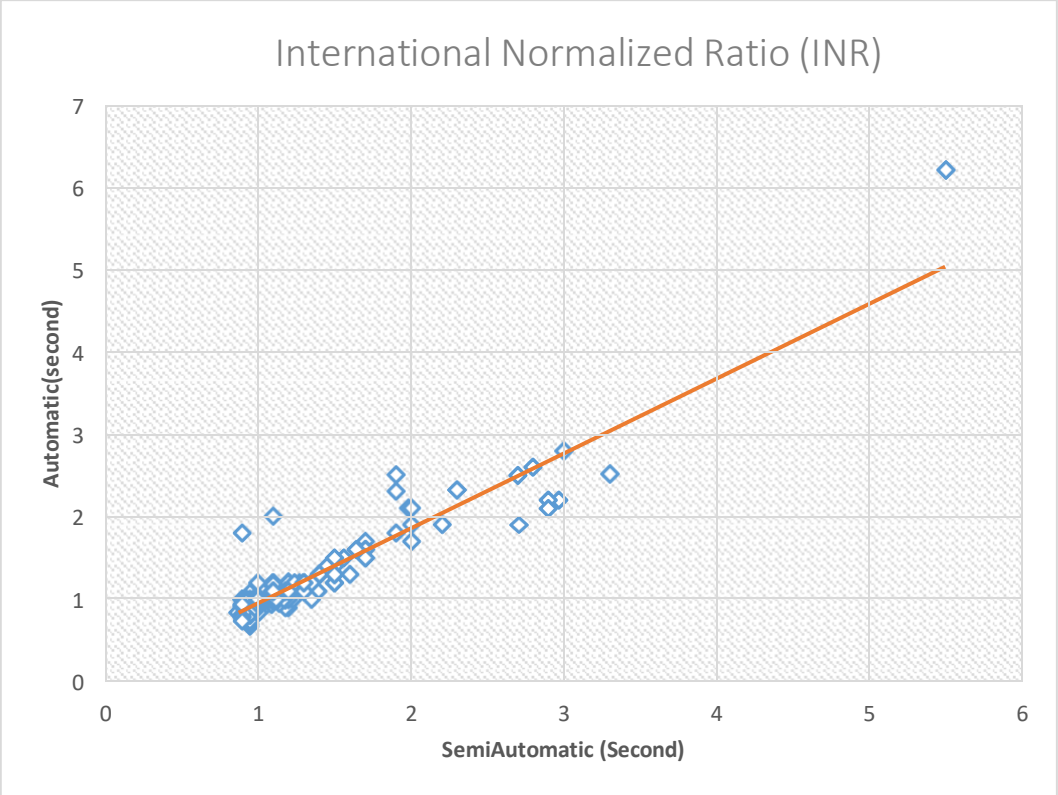
Table-13: Correlation coefficient between aPTT and INR (Semi-automatic)-correlations

			ATPP	INR
Spearman's rho	ATPP	Correlation Coefficient	1.000	.408**
		Sig. (2-tailed)	.	.000
		N	250	250
	INR	Correlation Coefficient	.408**	1.000
		Sig. (2-tailed)	.000	.
		N	250	250

**. Correlation is significant at the 0.01 level (2-tailed).

In the present study, INR values were determined from capillary whole blood samples with the help of automatic and semi-automatic devices. The following Graph-6 shows there was a strong correlation between both devices.

Graph-6: Correlation of INR value between Automatic and semiautomatic.



We report prothrombin time between automatic and semi-automatic devices in the present study. Prothrombin time results of plasma collected from patients aged 1-20 years show a time range, i.e., 14.54 ± 4.01 sec in the automatic coagulometer while in the semi-automatic coagulometer, it was 13.51 ± 3.55 sec. In these age groups, we observed a non-significant difference between both devices. Similarly, in the age group between 21–40, prothrombin time in an automated coagulometer was 14.52 ± 5.40 sec and 13.51 ± 4.69 sec was found in a semi-automated coagulometer. P value, i.e., 0.14, shows a non-significant difference between these age groups. A statistically significant difference was found in the age group between 41-60 years, but the remaining included age groups reported a remarkably non-significant difference with both devices **(Table 14).**

Table-14: Distribution of Prothrombin Time (PT) between Automatic and semiautomatic in different age groups.

Age group (In Years)	Prothrombin Time (PT)		P-value
	ACL ELITE PRO (AUTOMATIC)	ERBA (SEMI AUTOMATIC)	
1- 20	14.54 ± 4.01	13.51 ± 3.55	0.16 [NS]
21-40	14.52 ± 5.40	13.51 ± 4.69	0.14 [NS]
41-60	13.81 ± 2.50	12.79 ± 2.33	0.04 [S]*
61-80	15.52 ± 8.33	14.62 ± 7.08	0.60 [NS]
81-100	13.33 ± 2.46	12.14 ± 2.57	0.36 [NS]

Mean ± Std. Dev., *=Significant

We report prothrombin time between automatic and semi-automatic devices in the present study. APTT results of plasma collected from patients aged 1-20 years show a time range, i.e., 28.66 ± 5.37 sec in the automatic coagulometer, while the semi-automatic coagulometer showed 26.13 ± 4.43. In these age groups, we observed a statistically significant difference between both devices. Similarly, in the age group between 21-40 years, APTT in automated coagulometer was 29.91 ± 9.68 sec, and 27.21 ± 7.74 sec was found in semi-automated coagulometer. P value, i.e., 0.02, shows the statistically significant difference between these age groups. Whereas statistically non-significant difference was found in age groups between 41-60, 61-80 and 80-100 years, respectively, as shown in **Table -15.**

Table-15: Distribution of APTT between Automatic and semiautomatic in different age groups.

Age group (In Years)	Activated Partial thromboplastin Time (APTT)		P-value
	ACL ELITE PRO (AUTOMATIC)	ERBA (SEMI AUTOMATIC)	
1- 20	28.66 ± 5.37	26.13 ± 4.43	0.011 [S]*
21-40	29.91 ± 9.68	27.21 ± 7.74	0.02 [S]*
41-60	29.06 ± 6.62	27.01 ± 5.93	0.11[NS]
61-80	30.05 ± 9.71	27.74 ± 8.82	0.26 [NS]
81-100	27.95 ± 3.60	25.70 ± 3.29	0.21 [NS]

Mean ± Std. Dev., *=Significant

In Table 13, in the age group 1-20 years, the INR ratio was approximately 1.21 ± 0.38 seconds in automatic coagulometers and 1.13 ± 0.28 seconds in semi-automatic coagulometers. According to the P value of 0.29, there was no significant difference between the two age groups. Similarly, all other age groups, including 21-40, 41-60, 61-80 and 81-100 years, showed a statistically non-significant difference concerning the INR **(Table 16).**

Table-16: Distribution of International Normalized Ratio (INR) between Automatic and semiautomatic in different age groups.

Age group (In Years)	International Normalized Ratio (INR) in second		P-value
	ACL ELITE PRO(AUTOMATIC)	ERBA (SEMI AUTOMATIC)	
1- 20	1.21 ± 0.38	1.13 ± 0.28	0.29 [NS]
21-40	1.23 ± 0.47	1.15 ± 0.41	0.18 [NS]
41-60	1.16 ± 0.22	1.09 ± 0.22	0.12 [NS]
61-80	1.32 ± 0.76	1.30 ± 0.86	0.91 [NS]
81-100	1.13 ± 0.20	1.01 ± 0.19	0.25 [NS]

Mean ± Std. Dev., *=Significant

A total of 163 regular patients showed a 1.02 mean INR in the automated coagulometer. Whereas in 73 patients, INR values occurred between 1.2 and 1.9 seconds, which had a mean INR of 1.36, while 11 patients were found in the range of 2.0-2.9 in which 2.49 mean INR was obtained, as well as two patients were observed in the range between 3.0-3.9, which had a mean of 3.15. Only one patient was shown in the range between 4 and above, in which 5.5 mean INR was obtained. In contrast with the semi-automatic machine, mean INR was found in 187, 49, and 13 patients showing 0.99, 1.36, and 2.32 seconds respectively (Table 17).

INR values	Automatic (No. of patients)	Mean INR	Semi-Automatic (No. of patients)	Mean INR
Normal patients	163	1.02	187	0.99
1.2 - 1.9	73	1.36	49	1.36
2.0 -2.9	11	2.49	13	2.32
3.0 -3.9	2	3.15	0	0
4.0- above	1	5.5	1	6.2

Table-17: Different INR levels in automatic and semiautomatic

DISCUSSION:

In the last few decades, laboratory PT testing has become increasingly automated and semi-automated in India, the UK, and other countries. Over from 1987 maximum number of hospitals were using automated instruments for their routine work. Numerous laboratory instruments are based on the different principles of end-point detection.

This present prospective study was conducted in our Department of Pathology at BLDE (Deemed to be University) Shri B.M. Patil Medical College, Hospital, enrolling a total of 250 samples. In the present work, the INR results of the portable ACLPRO ELITE instrument compared well with semi-automated (ERBA ECL 105) instrument. ACLPRO ELITE coagulometer provides rapid and reliable INR examination for the clinical management of patients.

A semi-automated coagulometer for INR testing needs an adequate amount of blood collection and plasma separation by centrifugation, which requires considerable time and workload. Whereas patients and their healthcare providers use automatic coagulometers more frequently, they are increasingly used for self-testing.

In our series, 134 (54%) participants were male, and 116 (46%) were female, with a mean age of 37.66 ± 21 years. Similar results were found in a recent study by **Patil P et al. (2022). [55] In** this study, 100 samples were obtained from patients, and 95 samples out of 100 were included in the analysis. The remaining five samples were excluded from the study because of an insufficient volume of PPP. The mean age of study participants was 44 years, and the male-to-female ratio was found to be 0.9:1.

[55] Another study by **Kaur M et al. [56]** included 91.8% of the adult population, with a mean age of 44 ± 18.2 years.

In our study, the comparison between the INR results of the ACLPRO ELITE and ERBA ECL found a considerably high correlation among both the devices and Pearson's coefficient for the correlation between INR values was very high at 0.952 with $p<0.01$. Similar results were obtained by **Sharma P et al. 2021 [57]**. The comparison between the automated coagulometer and laboratory method found a considerably high correlation among these procedures. Pearson's coefficient for the correlation between INR and value was very high at 0.948 with a p-value <0.01.

A correlation coefficient greater than 0.7 indicates a significant correlation between two variables; the highest degree of correlation possible is 1.0. Moreover, the mean difference between INR measurements increased as the mean INR values increased. These results were comparable with the study by **Kalcik M et al. [58]**. Some other studies by Donaldson et al. show that the higher the INR value and the study obtained, the lower the correlation between the methods studied. **[59**

The present study revealed that the mean difference of INR obtained by automated coagulometer compared to semi-automated coagulometer testing was 0.068. They examine 250 INR samples, and our results show correlation coefficients of 0.96 for INR <2 and 0.93 for 2-3.5. These results compare with **Meneghelo et al. [60],** who conducted the study with 219 INR samples, and the findings of their study revealed correlation coefficients of 0.91 for INR less than 2, while 0.85 shown for INR of 2-3.5 and 0.71 for INR >3.5.

In diagnostic laboratories, the assessment of PT and APTT is the most commonly used test. Various methods are used to measure PT, APTT and INR scores, including

automated, semi-automated, and manual procedures. According to **Furlanchello T et al. [61],** automated and manual methods were also applied to assess PT and APTT scores. A similar report was revealed by **SallyAnne L et al. [62]** in **2017.**

This study's findings suggested a slight difference in the mean value of the automated coagulometer and semi-automated coagulometer for PT (*P value* <0.05) and an increase in the mean of APTT. This is comparable to the study done by **Jubair, MA.[63]**

In some previous literature [64]

numerous instruments have been studied for blood coagulation tests, and their working principle was also discussed briefly. In contrast, in this present research work, the blood coagulation technique and the accuracy of results among semi-automated and automated coagulometers are presented.

Evaluation of the INR report is essential to standardizing laboratory measurement values, especially for monitoring anticoagulant therapy such as warfarin.

Our findings show that APTT and INR have been noted with a correlation coefficient. This suggests that APTT increases, and then INR values increase, as shown in **Table 8.** On the other hand, semi-automatic machines showed a strong positive correlation between PT and INR.

Based on the present findings, we suggest that the INR value increases. As a result, Prothrombin Time also increased. These results were comparable with the study done by **Valerine et al. and Backer et al.[65] t**hey stated the high degree of correlation in automated analysis with PT with the help of two different thromboplastins.

In the present investigation, the PT/INR score provides good agreement with more demanding ISI calibrations. PT/INR score was diagnosed with the help of coagulometers. A two-stage derivation of INR was required, including the local PT, and this was employed to evaluate INR using the PT/INR line calculation. According to a study done by **Poller L et al**., **[66]** the use of an online spreadsheet simplifies the derivation of INR.

In our present study, the baseline PT, INR and APTT values in the ACL Elite Pro (Automatic) coagulometer were 14.51 ± 5.29 seconds, 1.22 ± 0.47 seconds and 29.47 ± 8.30, respectively. Semi-automatic instruments showed 13.5 ± 4.60 seconds, 1.15 ± 0.46 seconds and 27 ± 6.96 seconds, respectively. The comparison between automatic and semi-automatic coagulometers showed a statistically significant difference between both instruments. Similar results were found by **Parag Patil et al. [67]** when they compared PT < INR and APTT values between Group 1 and Group 2. According to group -1 the baseline PT, INR and APTT values were seen 12.1 sec, 1.06 sec and 26.5 sec respectively, while in group-2, the baseline PT, INR and APTT values were found to be 19.1 sec, 1.80 sec and 36.0 sec, respectively.

In **2016 Tripodi A et al. [68]** stated that, since ancient times, APTT values have been described as clotting times in seconds but not as percentage activity. Historically, APTT results are presented as clotting times (seconds), not per cent activity, as for PT.

Another study by **Condrey JA et al. [69]** performed on plasma samples collected from 30 healthy adult men and 30 healthy adult women had PT results of 86-100% and an aPTT result of 32-42 seconds. Both outcomes were within the current reference range (PT 70-140% aPTT 30-45 sec).

The overall incidences observed in this study show that there was a slight difference between the mean of automated and semi-automated coagulometers for PT, i.e., p-value represented $p<0.05$, and an increase in the mean of APTT for the automated coagulometer as compared to the semi-automated instrument (p-value <0.05). It represents a significant variation between the automated and semi-automated coagulometer methods for detecting PT, APTT, and INR ratio.

Our study recommended that an automated coagulometer (ACL) works on a photo-optical end-point detection method to analyze coagulation tests, including PT and APTT. The agreement between automated coagulation instruments was consistent in blood samples.

CONCLUSION

This present study shows a good agreement between automated and semi-automated instruments based on mechanical end-point detection method and photo-optical end-point detection method for assessing coagulation tests, including PT, aPTT and INR values. The agreement between automated coagulation analyzers was consistent in the samples included in our study. The present study compares PT/INR values using automated and semi-automated coagulometers. Both instruments, regarding their efficiency and accuracy in performance though automated, provide a slight edge over semi-automated in terms of being used as the gold standard for measuring PT, aPTT and INR ratio. Moreover, ACL has an important feature: it can determine fibrinogen concentrations through plasma measurements while it tests PT without additional cost in reagents or procedures. This instrument is a convenient and reliable tool for INR monitoring in routine laboratory examinations.

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IEC/NO-09/2021
Date - 22/01/2021

B.L.D.E. (DEEMED TO BE UNIVERSITY)
(Declared vide notification No. F.9-37/2007-U.3 (A) Dated. 29-2-2008 of the MHRD, Government of India under Section 3 of the UGC Act, 1956)
The Constituent College
SHRI. B. M. PATIL MEDICAL COLLEGE, HOSPITAL AND RESEARCH CENTRE

INSTITUTIONAL ETHICAL CLEARANCE CERTIFICATE

The Institutional ethical committee of this college met on 11-01-2021 at 11-00 am to scrutinize the synopsis of Postgraduate students of this college from Ethical Clearance point of view. After scrutiny the following original/corrected and revised version synopsis of the Thesis has been accorded Ethical Clearance

Title: A comparative study of INR values between automatic (ACL ELITE PRO) and semi automatic (ERBA) coagulometers

Name of PG student: Dr Ruchir Uttam, Department of Pathology

Name of Guide/Co-investigator: Dr Prakash.M.Patil , Associate Professor of Pathology

DR .S.V.PATIL
CHAIRMAN, IEC
Institutional Ethical Committee
B L D E (Deemed to be University)
Shri B.M. Patil Medical College,
VIJAYAPUR-586103 (Karnataka)

Following documents were placed before Ethical Committee for Scrutinization:

1. Copy of Synopsis / Research project
2. Copy of informed consent form
3. Any other relevant documents.

9

ANNEXURE- II

B.L.D.E (Deemed to be University),

SHRI B. M. PATIL MEDICAL COLLEGE HOSPITAL AND RESEARCH CENTER,VIJAYAPURA-586103

INFORMED CONSENT FOR PARTICIPATION IN DISSERTATION/RESEARCH

I, the undersigned,_____,S/OD/O W/O _____,aged _____years, ordinarily resident of_____do hereby state/declare that Dr._____of Hospital has examined me thoroughly on at_____(place) and it has been explained to me in my own language that I am suffering from _ ____disease (condition) and this disease/condition mimic following diseases . Further Doctor informed me that he/she is conducting dissertation/research titled__under the guidance of Dr._____requesting my participation in the study. Apart from routine treatment procedure, the pre-operative, operative, post-operative and follow-up observations will be utilized for the study as reference data.

Further Doctor has informed me that my participation in this study help in evaluation

of the results of the study which is useful reference to treatment of other similar cases in near future,and also I may be benefited in getting relieved of suffering or cure of the disease I am suffering.

The Doctor has also informed me that information given by me, observations made/ photographs/ video graphs taken upon me by the investigator will be kept secret and not assessed by the person other than me or my legal hirer except for academic purposes.

The Doctor did inform me that though my participation is purely voluntary, based on information given by me, I can ask any clarification during treatment / study related to diagnosis, procedure of treatment, result of treatment or prognosis. At the same time I have been informed that I can withdraw from my participation in this study at any time if I want or the investigator can terminate me from the study at any time from the study but not the procedure of treatment and follow-up unless I request to be discharged.

After understanding the nature of dissertation or research, diagnosis made, mode of treatment,I the undersigned Shri/Smt_____under my full conscious state of mind agree to participate in the said research/dissertation.

Signature of patient:

Signature of doctor:

Witness: 1.

2.

Date:

Place:

MASTER CHART

			ACL ELITE PRO (AUTOMATIC)			ERBA (SEMI AUTOMATIC)		
SR.No.	**Age**	**Gender**	**PT**	**APTT**	**INR**	**PT**	**APTT**	**INR**
1	40	M	21.9	42.1	1.9	20.9	39.1	1.8
2	83	F	14	35.1	1.2	13.1	32.7	1.1
3	60	M	13.5	28.4	1.1	11.7	26.7	1
4	42	M	13.5	23.9	1.1	12.7	21.3	1.1
5	42	M	13.9	23.5	1.2	11.9	21.7	1
6	68	M	11.4	28.3	0.9	11.4	24.8	0.99
7	19	M	12.9	27.2	1.1	11.6	29.8	1
8	65	F	14.4	30.5	1.2	12.5	28.7	1.09
9	80	M	16.6	33.6	1.4	15.1	31.3	1.3
10	54	M	15.3	34.9	1.3	13.4	31.1	1.1
11	22	F	13.4	26.1	1.1	13.2	25.4	1.1
12	35	F	20.2	32.3	1.7	18.9	28.7	1.7
13	23	M	15.3	25.7	1.3	13.5	23.1	1.1
14	12	M	14.2	29	1.1	12	26.7	1
15	20	F	13.6	23.9	1.1	21.7	21.3	2
16	20	F	14.3	19.2	1.25	12.8	18.9	1.1
17	30	F	11.2	28	0.9	11.5	27.3	1
18	39	M	13.7	30.8	1.2	11.3	26.8	0.9
19	21	M	11.1	47.3	0.9	11.5	41.4	1
20	25	F	14.4	25.4	1.2	14.5	28.4	1.2
21	4	M	14.2	29	1.1	14	26.4	1.2
22	9	F	13.5	26.6	1.18	11.3	23.9	0.9
23	35	M	11.6	29.4	0.92	11.5	24.9	1
24	11	M	14.2	29	1.1	13.1	27.4	1.1
25	70	M	20.1	41.8	1.7	18.4	36.5	1.6
26	24	F	30.8	37	1.9	27.3	31.1	2.5
27	25	M	19.4	26.5	1.7	17.3	24.5	1.5
28	17	M	15.8	30	1.39	13.2	27.3	1.1
29	50	M	17.2	23	1.5	15.3	19.8	1.3
30	17	M	15.8	30	1.39	12.8	24.7	1.1
31	38	M	15	25.5	1.3	14.5	24.4	1.2
32	45	F	12	30.9	1	11.5	28.9	1
33	24	F	30.7	52.9	2.7	26.7	46.7	2.5
34	32	M	14.5	24.1	1.2	13.1	23.7	1.1
35	40	M	12.6	28.9	1.1	11.9	26.6	1.03

36	52	F	11.3	28	0.98	10	26.7	0.85
37	21	F	14.2	27.8	1.2	13.2	24.1	1.1
38	64	M	11	28.5	0.9	11.5	25.7	1
39	36	M	12.7	27.6	1.1	11.6	27.1	1
40	28	F	14.3	29.1	1.2	12.9	29.7	1.12
41	38	F	21	48.6	1.9	26.5	37.4	2.3
42	30	F	13	27.5	1.13	11.3	24.9	0.98
43	36	F	12.7	27.5	1.1	12.1	26.4	1
44	59	F	15.9	28.6	1.4	15.4	27.9	1.3
45	29	M	13.1	31.2	1.1	12.5	29.9	1
46	63	F	12.2	25	1	11.7	23.6	1
47	9	F	13.5	26.6	1.18	12.3	25.6	1
48	35	M	11.6	29.4	0.9	10.3	28.9	0.88
49	33	F	17.7	23	1.56	16.7	22.7	1.5
50	52	M	11.5	27.6	1	10.6	27.5	0.91
51	57	M	15.6	22.5	1.3	13.9	21	1.2
52	66	M	12.5	22	1	11.8	20.6	1
53	61	M	14.7	28.1	1.2	13.9	26.2	1.21
54	71	F	14.8	22.5	1.3	14.1	19.7	1.2
55	61	M	15.4	31.9	1.3	12.6	24.8	1.1
56	30	M	26.2	47.9	2.3	24.9	43.1	2.3
57	56	M	13.9	26.6	1.2	12.7	25.1	1.1
58	63	F	17	28.1	1.5	14.1	26.9	1.2
59	65	M	13.8	25	1.2	12.1	23.9	1.04
60	29	F	11	22.3	0.95	11.5	19.8	1.08
61	39	M	14.3	24.9	1.2	11.9	26.9	1
62	23	F	11	22.3	0.95	11.5	21.3	1
63	51	F	11.6	22.3	1	11.4	19.4	0.99
64	49	M	12.5	24	1	11.8	23.7	1
65	41	M	13.2	22.8	1.1	12.7	19.5	1.1
66	66	F	11.8	24.8	1	11.5	23.7	1
67	26	F	13.4	28.3	1.1	13	26.1	1.1
68	36	M	32	49.7	2.8	28.2	41.5	2.6
69	61	F	15.2	32.8	1.3	14.1	29.3	1.2
70	70	M	11.6	32.2	0.9	20.9	36.6	1.8
71	68	F	33.5	51	3	29.5	47.8	2.8
72	25	F	12	26.6	1.04	11.4	23.4	0.99
73	56	M	14.8	30.7	1.3	14.5	29.1	1.2
74	27	F	11	24	0.9	11.5	23.1	1
75	61	M	14.7	28.1	1.2	13.9	27.3	1.2
76	27	M	19.4	22.8	1.7	18.5	20.9	1.6
77	50	M	11.8	39.4	1	11.5	36.7	1

78	52	M	12.3	29.6	1	11.9	28.1	1
79	24	F	11	21.7	0.95	10.2	19.6	0.87
80	27	F	11.1	23.3	0.9	9.7	21.8	0.82
81	27	F	11.1	26.1	0.9	11.8	31.2	1
82	71	M	14.1	28.9	1.2	13.7	28.4	1.2
83	51	F	12.7	31.7	1.1	12.4	30	1
84	23	F	11.1	26.1	0.9	10.1	24.1	0.86
85	20	F	11.1	28.6	0.9	11	27.9	0.9
86	23	F	12.1	28.3	1	11.5	26	1
87	14	F	13.5	26.6	1.18	12.8	24.9	1.1
88	9	M	14.2	29	1.1	13.6	25.7	1.2
89	45	M	11.6	29.4	0.92	11.4	27.6	0.99
90	8	M	14.2	29	1.1	12.3	25.9	1
91	76	F	14.1	26.4	1.23	13.2	24.7	1.1
92	22	M	12.8	28.1	1.1	12.1	26.6	1
93	19	M	12.8	24.4	1.1	12.5	23.6	1.1
94	22	F	11.5	28.4	1	11.5	28.1	1
95	10	M	14.2	29	1.1	13.2	26.5	1.1
96	36	M	11.8	27.7	1	11.3	24.9	0.97
97	80	F	13	34.1	1.14	12.8	33.1	1.1
98	45	M	11	22.8	0.95	8.39	21.4	0.68
99	50	M	17.8	52.2	1.5	15.9	46.6	1.4
100	36	M	13.1	20	1.14	11.1	18.5	0.95
101	55	F	22.5	29.2	1.98	21.7	27.9	2.1
102	88	F	11.7	31	1.01	10.1	27.4	0.85
103	52	M	13.8	31.9	1.2	12.8	28.3	1.1
104	63	M	60.8	77.3	5.5	52.7	69.7	6.2
105	68	M	13	29.6	1.13	11.7	28.9	1
106	68	F	23.3	36.9	2	21.1	31.4	1.9
107	9	F	16.6	39.3	1.45	15.7	34.5	1.4
108	60	M	17.2	42.4	1.5	16.8	38.7	1.5
109	47	M	12.9	27.2	1.1	11.5	26.1	1
110	22	F	14.1	23.2	1.2	13.9	19.5	1.2
111	35	F	19.6	76.6	1.7	17.5	63.7	1.5
112	65	F	11.6	24	1	12.3	24.8	1
113	36	M	23.4	54.5	2	22.6	47.1	2.1
114	81	M	11.4	23.8	0.9	10.7	21.9	0.92
115	18	M	18.5	40.3	1.64	17.9	34.3	1.6
116	91	M	14.5	25.8	1.27	13.7	23.7	1.2
117	22	F	11.2	22.3	0.9	9.23	19.3	0.78
118	27	F	15.5	22.6	1.3	14.2	21.1	1.2
119	92	M	11	27.9	0.95	8.39	25.7	0.7

120	34	F	11	22.2	0.95	8.76	21.1	0.74
121	21	F	12.8	24.8	1.18	11.8	24.1	1.02
122	29	F	11.5	22.5	0.97	11.5	19.2	1
123	46	F	16.9	22.6	1.4	15.4	21.3	1.3
124	53	M	16.6	30.6	1.4	15.2	29.6	1.3
125	91	M	14.5	25.8	1.27	13.5	23.8	1.1
126	21	F	11.3	27.8	0.98	10.4	24.3	0.89
127	29	F	12.2	24.6	1.06	10.9	23.6	0.94
128	24	F	11.1	30	0.87	9.87	25.4	0.84
129	61	M	12.5	22.9	1.09	10.9	21.4	0.94
130	31	F	11.6	25.6	1.01	11.3	24.1	0.98
131	21	F	11	24.5	0.95	11	23.1	0.95
132	22	F	11.4	22.1	0.99	10.5	21.1	0.92
133	45	F	12.1	28.7	1.05	11.7	26.7	1
134	76	M	11.6	27.7	1	11.1	23.1	0.96
135	29	F	13.2	23.5	1.1	11.8	22.2	1
136	20	F	11	22.4	0.95	9.14	19.3	0.81
137	38	F	12.6	25.2	1.1	11.6	22.5	1
138	18	M	12.5	24.9	1	11.9	24.2	1
139	53	M	14.4	25.4	1.2	13.9	23.8	1.1
140	46	F	13.6	24.3	1.1	12.4	24.1	1
141	81	M	11.4	28.3	0.99	11.1	26.1	0.96
142	38	M	11.6	29.4	0.92	11.3	26.7	0.98
143	40	M	11.6	29.4	0.92	11.2	26.1	0.97
144	42	M	11.6	29.4	0.92	11.4	28.3	0.99
145	23	F	11.1	26.1	0.9	10.8	24.4	0.94
146	23	F	12.1	28.3	1	12	27.5	1
147	14	F	13.5	26.6	1.18	13.1	25.5	1.1
148	9	M	14.2	29	1.1	13.7	27.1	1.1
149	19	M	12.8	24.4	1.1	11.9	24.1	1
150	76	F	14.1	26.4	1.23	12.6	25.6	1
151	22	M	12.8	28.1	1.1	11.7	26.1	1
152	32	M	12	31.1	1	11.8	26.5	1
153	45	M	11.6	29.4	0.925	10.3	26.8	0.9
154	36	M	11.8	27.7	1	10.9	25.4	0.95
155	67	M	11.7	20.7	1.02	11.1	17.8	0.96
156	28	M	12.7	26.3	1.1	13.2	30	1.2
157	61	M	13.1	22.7	1.1	12.6	21.1	1
158	34	F	14.1	28.5	1.2	13.9	27.5	1.1
159	58	M	11.2	25.3	0.9	9.31	24.1	0.82
160	24	F	14.9	32.8	1.3	12.9	26.7	1.1
161	12	F	13.5	26.6	1.18	12.7	23.8	1
162	22	F	11	31.5	0.9	8.92	25.9	0.79

163	45	M	11	22.8	0.95	9.64	21.7	0.85
164	23	F	11.7	30.7	1.02	11.5	25.1	1
165	35	F	12.3	31.9	1.07	11.6	27.5	1
166	33	M	11.6	29.4	0.925	11.5	29.1	1
167	38	M	11.6	29.4	0.925	9.96	23.2	0.87
168	59	M	14	26.9	1.2	13.1	25.6	1.1
169	9	F	13.5	26.6	1.18	12.7	26.2	1
170	40	M	36.4	51.8	3.3	32.8	42.6	2.5
171	23	F	24.9	64.7	2.2	24	53.5	1.9
172	19	F	32.8	48.4	2.97	28.7	42.7	2.2
173	45	M	11.6	29.4	0.925	11.5	27.3	1
174	23	F	12.6	28.2	1.1	12.3	27.8	1
175	9	F	14.2	29	1.1	13.7	28.1	1.1
176	12	M	14.2	29	1.1	13.7	28.1	1.1
177	8	M	14.2	29	1.1	13.6	27.3	1.16
178	25	F	11	26.4	0.95	9.34	24.6	0.82
179	26	M	17.9	37	1.5	14.5	34.5	1.2
180	25	F	11.1	23.8	0.9	10.5	22.1	0.92
181	46	M	11.6	29.4	0.925	11.1	28.4	0.96
182	25	F	11.3	25.7	0.98	11.5	24.1	1
183	64	M	13	21	1.13	11.6	16.9	1
184	22	F	13.5	26.6	1.18	12.7	24.7	1.09
185	28	M	11.6	29.4	0.925	10.7	27.9	0.93
186	22	F	13.5	26.6	1.18	11.9	23.6	1
187	23	M	12.2	31.8	1.06	11.8	31.1	1
188	50	M	17.8	52.2	1.5	15.7	47.9	1.3
189	30	M	11	28.3	0.9	8.89	26.1	0.79
190	22	M	12.2	31.8	1.06	11.6	29.6	1
191	24	F	15.5	27	1.35	12	27.9	1
192	36	M	13.1	20	1.14	12.9	17.5	1.1
193	80	M	16.9	26.1	1.4	15.8	26	1.3
194	64	M	11.5	26.5	1	11.4	25.3	0.99
195	48	F	13.7	23.9	1.19	13.2	19.8	1.1
196	70	M	13.3	30	1.1	12.8	27.6	1.1
197	38	M	12.1	33.3	1	11.9	26.5	1
198	23	F	11	21.4	0.9	10.5	17.5	0.92
199	19	F	13.5	26.6	1.18	12.5	23.5	1
200	8	M	14.2	29	1.1	13.3	23.4	1.1
201	23	F	12	22.4	1	11.4	22.8	0.9
202	24	F	13.1	24.8	1.1	12.7	22.7	1
203	61	M	12.5	28.8	1	13.8	25.7	1.2
204	36	M	11.6	29.4	0.925	11.5	25.3	1
205	10	M	14.2	29	1.1	14.1	28.4	1.2

206	19	F	11.8	24	1	11.5	23.1	1
207	12	M	14.2	29	1.1	12.7	26.4	1.07
208	77	M	12.6	29.3	1.09	11.9	28.1	1.03
209	25	M	15.9	26.8	1.3	14.8	26.5	1.2
210	24	F	11	22	0.94	10.3	18.4	0.9
211	8	M	14.2	29	1.1	13.9	27.3	1.18
212	22	F	13.5	20.2	1.2	12.9	22	1.12
213	26	F	11	21.4	0.9	10.8	19.8	0.94
214	25	F	14	22	1.22	13.8	19.7	1.1
215	70	M	13.2	27.1	1.1	11.3	23.1	0.98
216	30	F	11.7	20.3	1	11.3	16.3	0.98
217	12	F	13.5	26.6	1.18	12.7	23.8	1
218	13	M	14.2	29	1.2	14.1	28.3	1.2
219	52	M	13.8	31.9	1.2	12.1	29.8	1
220	30	M	11.6	29.4	0.925	11.5	25.3	1
221	22	F	14.1	23.2	1.2	13.5	20.2	1.1
222	31	F	32.9	42.8	2.9	25.4	40.5	2.2
223	45	F	15.5	32.9	1.35	14.7	27.3	1.2
224	19	F	11.3	24.5	0.98	10.3	22.2	0.9
225	61	M	11.4	29.3	0.991	11.1	27.3	0.96
226	68	M	13	29.6	1.13	12.3	26.9	1
227	20	F	13.5	31.6	1.17	11.8	27.5	1
228	27	M	11.6	29.4	0.925	11.2	29.3	0.97
229	12	F	13.5	26.6	1.18	13.2	23.7	1.1
230	47	M	12.9	27.2	1.1	12.2	26.1	1
231	10	F	13.5	26.6	1.18	12.9	26.4	1.1
232	10	M	14.2	29	1.1	11.4	24.4	0.99
233	33	F	13.3	29.3	1.1	12.4	28.1	1
234	35	M	12.9	32.4	1.12	11.5	27.3	1
235	1	M	32.7	48.1	2.9	26.8	39.9	2.1
236	22	F	31.4	51.1	2.7	23.7	42.8	1.9
237	12	M	14.2	29	1.1	12.9	26.8	1.1
238	75	M	14.3	22	1.24	14.1	20.9	1.2
239	1	F	15	31.9	1.3	13.9	24.7	1.1
240	92	M	18.2	25.9	1.5	16.6	24.3	1.3
241	45	F	11.6	23.9	1	11.9	24.6	1
242	18	F	11	22.3	0.9	8.27	17.3	0.74
243	22	F	23.2	55.3	2	21.3	44.5	1.7
244	60	M	11	24	0.9	10.8	23.1	0.94
245	20	F	13.5	25.2	1.1	12.8	23.7	1.1
246	52	M	19	32.9	1.6	15.7	29.2	1.3
247	12	M	14.2	29	1.1	13.1	23.7	1.1

248	75	F	15.5	40.8	1.3	14.1	34.4	1.2
249	20	M	12.6	25.9	1	11.5	24.4	1
250	47	M	14.7	30.6	1.2	13.7	26.5	1.1

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