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Literature Review

Literature Study on Factors Influencing the Biochemical Analytes Stability in Blood, Serum and Plasma: Systematic Review

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Abstract: Blood testing represents an essential phase in diagnosis and treatment. It is important to comprehend the biochemical analytes' stability. This research gathers information from different journals that have investigated the stability of biochemical analytes under different conditions. This research aims to collect and analyze data about conditions that promote stability, conditions that lead to instability, and how stability varies in different tubes. By combining the outcomes of these studies, this research aims to deliver a complete overview of the ability of biochemical analytes to remain unchangeable in various contexts. In this review study, we collected all articles studying pre-analytical stability. A PubMed and Web of Science search was performed with a time limit of 2005-2021 using the following keyword: "(Stability) and (biochemical laboratory tests)". 375 articles were obtained and we selected 20 articles according to the titles, abstracts, and indexation. In the 20 included references, 31 analytes were ranked according to the most frequently studied analytes: Creatinine, Alanine Aminotransferase (ALT), triglycerides, urea, cholesterol, Alkaline Phosphatase (ALP), lactate dehydrogenase, Aspartate Aminotransferase (AST), total bilirubin, gamma-glutamyltransferase, albumin, sodium, High-Density Lipoprotein (HDL), potassium, calcium, total protein, creatine kinase, uric acid, glucose, C-Protein Reactive (CRP), amylase, ferritine, magnesium, lipase, iron, chloride, direct bilirubin, Low-Density Lipoprotein (LDL), phosphate, transferrin, carbon dioxide (CO_2). Before centrifugation, creatinine, urea, Alkaline Phosphatase (ALP), total bilirubin, albumin, total protein, lipase, chloride, direct bilirubin, phosphate, and Carbon Dioxide (CO_2) were stable in whole blood at room temperature for up to 24 h. All the analytes in the plasma were stable except for potassium and AST. In serum, ALP, lipase, chloride, direct bilirubin, total bilirubin, LDL, Carbon Dioxide (CO_2), triglyceride, cholesterol, total protein, creatinine kinase, C-Reactive Protein (CRP), and transferrin were stable at room temperature, refrigerated temperature, and freezing temperature. Aspartate Aminotransferase (AST), Gamma-Glutamyl Transferase (GGT), Lactate Dehydrogenase (LDH), creatinine, glucose, and urea were unstable after cycles of freezing and thawing at -196°C. These analytes show important stability after cycles of freezing and thawing at -20°C, except for Lactate Dehydrogenase (LDH). We noticed after the comparison of the two collection tubes, the Plasma Separation Tube (PST II)" and the Serum Separation Tube "SST (SST II)", the instability of total protein, ferritine, phosphate, aspartate Aminotransferase (AST), total and direct bilirubin and calcium. This study summarizes the outcomes of 20 stability studies to generate maximum stability information.

Keywords: Pre-Analytical Variations, Biochemical Analytes, Plasma, Serum, Stability, Whole Blood

Introduction

Blood testing represents an essential phase in diagnosis and treatment. It's subdivided into three important phases: Pre-analytical phase, analytical phase, and post-analytical phase (Martins *et al*., 2018).

Depending on whether the errors occurred prior to, during, or following the analysis. The majority of errors take place before the test, during the pre-analytical phase since there are no established procedures for identifying and quantifying pre-analytical variables (Abdollahi *et al*., 2014).

Stability refers to how well a material can maintain its initial properties over a set time period while stored under specific conditions (Gómez Rioja *et al*., 2018).

A lot of factors alternate the stability of biochemistry parameters, such as time, coffee, alcohol, cigarettes, medicines pretreatment, transport, and storage (Ellervik and Vaught, 2015).

Some researchers study the stability at different times between blood collection and centrifugation and others study the stability during different storage conditions.

In this review, we also examined papers studying the effects of pre-analytical factors in biochemistry tests using blood, serum, and plasma fractions. For each biochemical parameter, we will identify the conditions of stability and instability according to the type of samples, the time, the temperature, and the type of tubes used.

Study Methods

Research Methodology

The research was conducted in PubMed and Web of Science with a time constraint (2005-2021), using the keywords "(stability) AND (biochemical laboratory tests)". Twenty essays were chosen from 375 articles with various themes.

Study Selection

The studies were chosen based on:

- The headings
- English-only articles
- The abstract
- Web of Sciences and Scopus only index articles
- Papers examining the consistency of biochemical assays

Stability Conditions

The papers chosen were classified according to these criteria:

- Sample type / Tube collection
- Metabolites
- Temperature and time
- Results

Results

From 2005-2021, 20 publications were chosen. The number of biochemical analytes varied from paper to paper, ranging from 2-30 (Fig. 1). The majority of research used healthy subject samples. The sample size ranged from 5-420 people.

The temperature range in the selected studies can be categorized into five categories:

→ (15-25°C)
→ 30-35°C
→ 2-10°C
→ Deep freezer (-10 to -30°C)
→ Cycles of freezing-thawing (Freezing can cause water to freeze first and lead to the accumulation of proteins and salt in the container's bottom. After thawing, the serum appears cloudy. Notably, repeated freezing-thawing cycles increase analyte variations (Gislefoss *et al*., 2017))

Several times were chosen by different studies from 30 min to 3 months. Different collection tubes were used during these studies: Lithium heparin, plasma separating tube, serum separation tube with gel and without gel, rapid serum tube, K2EDTA tube, and fluoride tube. All these tubes were chosen depending on samples: Whole blood, serum or plasma.

34 biochemical analytes were studied in the papers chosen. To ease the study, we listed these analytes in descending order of mention in the articles.

Creatinine

18 articles studied the stability of creatinine under various storage conditions. Accordingly, creatinine stability was variable in five articles in serum collected in SST with and without gel, especially when it is stored at 22°C or higher and during freezing-thawing cycles (Abraham *et al*., 2019; Tanner *et al*., 2008; Kar *et al*., 2013; Kang *et al*., 2013; Haslacher *et al*., 2017).

According to Zwart *et al*. (2009), Henriksen *et al*. (2014), Monneret *et al*. (2016), Dupuy *et al*. (2018b); Kang *et al*. (2013), creatinine was stable in whole blood stored at room temperature for up to 24 h. Plasma can be kept at room temperature for up to 12 h and refrigerated for up to 6 h (No study in this case uses more than 6 h for storage of plasma at refrigerated temperature for creatinine) (Monneret *et al*., 2016; Stahl and Brandslund, 2005; Leino and Koivula, 2009).

Fig. 1: Number of analytes per paper

In serum, studies by Dupuy *et al*. (2018b); Taylor and Sethi (2011); Cuhadar *et al*. (2012-2013); Ng and Yeo (2013); Kar *et al*. (2013); Kachhawa *et al*. (2017) have shown stability after storage at room temperature, refrigerated, and frozen for up to 3 months. We also noticed the stability of this analyte after freezing cycles at -20°C in studies conducted by Taylor and Sethi (2011); Cuhadar *et al*. (2013); Kang *et al*. (2013) (Tables 1-4).

Alanine Aminotransferase (ALAT)

18 articles study alanine aminotransferase stability in diverse storage conditions. In whole blood, ALAT was unstable at room temperature after 10 h of storage (Henriksen *et al*., 2014). The serum also shows reduced activity when it is stored at 25, 4, 0, 10, -20°C and during the freezing-thawing cycle at -20°C (Taylor and Sethi, 2011; Shimizu and Ichihara, 2019). ALAT was stable in other articles before centrifugation at room temperature for 24 h (Zwart *et al*., 2009; Monneret *et al*., 2016; Dupuy *et al*., 2018b; Kang *et al*., 2013), in serum stored at room temperature for 30 min up to 1 week, at refrigerated temperature up to 5 days, at -20°C for 3 months, after cycles of freezing and thawing and after temperature fluctuations (Dupuy *et al*., 2018b; Tanner *et al*., 2008; Cuhadar *et al*., 2012; 2013; Ng and Yeo, 2013; Kang *et al*., 2013; Kachhawa *et al*., 2017; Haslacher *et al*., 2017) (Tables 1-5).

Triglyceride

17 articles study triglyceride stability. Triglycerides were unstable in whole blood at room temperature for 10 h (Henriksen *et al*., 2014). Also, in another article, triglycerides were unstable after 3 cycles of freezing and thawing at -196°C (Kang *et al*., 2013).

Triglyceride was stable in whole blood at room temperature for 24 h, in plasma at room temperature up to 12 h (Monneret *et al*., 2016; Stahl and Brandslund, 2005; Leino and Koivula, 2009) and at refrigerated temperature for 48 h (Dupuy *et al*., 2018b; Leino and Koivula, 2009) and in serum at room temperature, at refrigerated temperature up to 56 days and at freezing temperature (-20°C) for 3 months (Abraham *et al*., 2019; Tanner *et al*., 2008; Taylor and Sethi, 2011; Cuhadar *et al*., 2012; 2013; Ng and Yeo, 2013; Kang *et al*., 2013; Shimizu and Ichihara, 2019; Parra-Robert *et al*., 2016). Other studies by Taylor and Sethi (2011), Cuhadar *et al*. (2013); Haslacher *et al*. (2017) have shown the stability of this analyte even after freezing-thawing cycles at -20°C and even 30°C temperature fluctuations (Tables 1-5).

Urea

16 articles study urea stability in various storage conditions. Urea was unstable in serum at 35°C for 24 h (Tanner *et al*., 2008), at 4°C and 24°C in serum collected in plain serum, and at 24°C in serum collected in SST (Cuhadar *et al*., 2012). Also, we noticed some variation after some freezing-thawing cycles (Cuhadar *et al*., 2013; Kang *et al*., 2013). The stability of this parameter was noted in whole blood following storage at room temperature for 24 h (Henriksen *et al*., 2014; Monneret *et al*., 2016; Dupuy *et al*., 2018b). In plasma stored at room temperature and refrigerated temperature, respectively, after 24 and 48 h (Monneret *et al*., 2016; Dupuy *et al*., 2018b; Stahl and Brandslund, 2005; Leino and Koivula, 2009). According to Taylor and Sethi (2011); Parra-Robert *et al*. (2016), serum was stable at room temperature up to 120 h. Ng and Yeo (2013); Kar *et al*. (2013) proved stability in refrigerated serum for up to 336 h. Haslacher *et al*. (2017) showed that serum remained stable after being stored frozen for 12 weeks and during free-thaw cycles at -20°C, also after temperature fluctuations (Tables 1-5).

Cholesterol

16 articles study the stability of cholesterol in various storage conditions. Most of the articles described cholesterol as stable under different conditions. Monneret *et al*. (2016), Dupuy *et al*. (2018b); Kang *et al*. (2013) reported whole-blood stability at room temperature for 24 h. In plasma, cholesterol was stable at room temperature for 12 h, as reported by Monneret *et al*. (2016), Stahl and Brandslund (2005); Leino and Koivula (2009), and at 4°C it remained stable for 48 h according to Dupuy *et al*. (2018); Leino and Koivula (2009). Additionally, serum cholesterol was stable at room temperature and under refrigeration up to 1 week according to Abraham *et al*. (2019); Tanner *et al*. (2008); Taylor and Sethi (2011); Cuhadar *et al*. (2012), Ng and Yeo (2013); Kang *et al*. (2013); Parra-Robert *et al*. (2016), after freezing for 3 months (Tanner *et al*., 2008; Cuhadar *et al*., 2012) and also after cycles of freeze-thaw and temperature fluctuations (Cuhadar *et al*., 2013; Haslacher *et al*., 2017). However, in one article, this parameter was unstable in whole blood collected in a lithium heparin gel tube and SST at room temperature for less than 10 h (Henriksen *et al*., 2014) (Tables 1-5).

Alkaline Phosphatase

16 articles study alkaline phosphatase stability. After analyzing all the articles chosen, ALP was stable in all conditions: In whole blood for 24 h at room temperature (Zwart *et al*., 2009; Henriksen *et al*., 2014; Monneret *et al*., 2016; Dupuy *et al*., 2018b), ALP stability in serum stored at room temperature and refrigerated temperature for 56 days was observed by Dupuy *et al*. (2018b); Tanner *et al*. (2008); Taylor and Sethi (2011); Cuhadar *et al*. (2012); Ng and Yeo (2013); Shimizu and Ichihara (2019);; Parra-Robert *et al*. (2016). According to Shimizu and Ichihara (2019), the stability was maintained at frozen temperatures for 3 months, while that according to Haslacher *et al*. (2017), was after cycles of freezing-

thawing at -20°C and temperature fluctuations. In plasma, different authors described ALP as stable at room temperature for 12 h and at 4°C for 72 h (Monneret *et al*., 2016; Shin *et al*., 2021; Dupuy *et al*., 2018b) (Tables 1-5).

Lactate Dehydrogenase (LDH)

16 articles study LDH's stability. LDH activity was variable in the different articles chosen. This analyte was unstable in 7 articles: Before centrifugation at 20-25°C for 12 h (Dupuy *et al*., 2018b; Kang *et al*., 2013), after centrifugation in serum stored at 35°C for 24 h (Tanner *et al*., 2008; Kang *et al*., 2013; Parra-Robert *et al*., 2016), at -20°C for 2 months and after cycles of freezing-thawing (Taylor and Sethi, 2011; Cuhadar *et al*., 2013). In other articles, LDH was stable in whole blood at room temperature for 10 h (Henriksen *et al*., 2014; Monneret *et al*., 2016), in serum at room temperature and 4°C up to 56 days (Taylor and Sethi, 2011; Cuhadar *et al*., 2012; Shimizu and Ichihara, 2019), at -30 for the same period (Haslacher *et al*., 2017) and after temperature fluctuation (Haslacher *et al*., 2017). In plasma, LDH was stable at room temperature for up to 12 h and at refrigerated temperatures for up to 72 h (Monneret *et al*., 2016; Stahl and Brandslund, 2005; Leino and Koivula, 2009; Dupuy *et al*., 2018a) (Tables 1-5).

Aspartate Aminotransferase (ASAT)

15 articles study the ASAT stability in various conditions. ASAT was unstable before centrifugation at room temperature for 1 h (Kang *et al*., 2013), in serum at 4-24°C for 48 h (Cuhadar *et al*., 2012), after freezing-thawing cycles at -196°C and after fluctuations (Kang *et al*., 2013; Haslacher *et al*., 2017). Also in other articles, ASAT was stable in whole blood for 24 h at room temperature (Zwart *et al*., 2009; Monneret *et al*., 2016; Dupuy *et al*., 2018b), in plasma at room temperature for 6 h (Monneret *et al*., 2016), and in serum stored at room temperature for 56 days, refrigerated for 56 days, and for 3 months frozen, according to Dupuy *et al*. (2018b); Tanner *et al*. (2008); Taylor and Sethi (2011); Cuhadar *et al*. (2013); Ng and Yeo (2013); Shimizu and Ichihara (2019); Parra-Robert *et al*. (2016). We noticed that ASAT was stable even after freezing cycles at -20°C (Taylor and Sethi, 2011; Cuhadar *et al*., 2013) (Tables 1-4).

Total Bilirubin

15 articles study total bilirubin stability. Total bilirubin shows instability after freezing-thawing cycles at -20°C (Cuhadar *et al*., 2013). In the other 14 articles, total bilirubin was stable in whole blood at RT for 24 h (Henriksen *et al*., 2014; Monneret *et al*., 2016; Dupuy *et al*., 2018b), in plasma at RT for 12 h and at 4°C for 6 h (No study in this case uses more than 6 h for storage of plasma at refrigerated temperature for total bilirubin) (Monneret *et al*., 2016; Stahl and Brandslund, 2005; Leino and Koivula, 2009). And in serum at RT for 56 days as found by Tanner *et al*. (2008), Taylor and Sethi (2011); Cuhadar *et al*. (2012); Shimizu and Ichihara (2019); Parra-Robert *et al*. (2016), at refrigerated temperature for 56 days (Dupuy *et al*., 2018b; Taylor and Sethi, 2011; Cuhadar *et al*., 2012; Ng and Yeo, 2013; Shimizu and Ichihara, 2019), between -30 and -10°C for 56 days (Taylor and Sethi, 2011; Shimizu and Ichihara, 2019). Also, this analyte remained stable after freezing cycles at -20°C and after temperature fluctuations (Taylor and Sethi, 2011; Haslacher *et al*., 2017) (Tables 1-5).

Gamma Glutamyltransferase (GGT)

15 articles study the GGT's stability in various conditions. GGT was unstable before centrifugation for 1 h, after centrifugation in serum stored at room temperature, and after cycles of freezing-thawing at -196°C (Kang *et al*., 2013). But in other articles using the same conditions, this analyte was stable: Before centrifugation at room temperature for 24 h (Henriksen *et al*., 2014; Monneret *et al*., 2016; Dupuy *et al*., 2018b), in plasma at room temperature for 24 h (Monneret *et al*., 2016; Stahl and Brandslund, 2005; Leino and Koivula, 2009) and at 8°C for 6 h (No study in this case uses more than 6 h for storage of plasma at refrigerated temperature for GGT) (Leino and Koivula, 2009). In serum at room temperature, refrigerated temperature, and freezing temperature for up to 56 days, these results have been found by several authors, including Dupuy *et al*. (2018b); Tanner *et al*. (2008); Taylor and Sethi (2011); Cuhadar *et al*. (2012); Cuhadar *et al*. (2013); Shimizu and Ichihara (2019); Parra-Robert *et al*. (2016). The stability was also noticed after cycles of freezing-thawing at -20°C and temperature fluctuations (Taylor and Sethi, 2011; Cuhadar *et al*., 2013; Haslacher *et al*., 2017) (Tables 1-5).

Albumin

14 articles study albumin stability. Albumin was unstable after centrifugation in serum stored at 4°C for 2-4 days (Ng and Yeo, 2013) and after cycles of freezing-thawing at -20°C (Cuhadar *et al*., 2013). In the other articles, albumin shows important stability in blood stored at room temperature for 24 h (Zwart *et al*., 2009; Henriksen *et al*., 2014; Monneret *et al*., 2016) and in plasma at room temperature and 8°C for 6 h (Henriksen *et al*., 2014; Stahl and Brandslund, 2005). In serum stored at room temperature up to 120 h (Abraham *et al*., 2019; Tanner *et al*., 2008; Taylor and Sethi, 2011; Cuhadar *et al*., 2012; Parra-Robert *et al*., 2016), refrigerated temperature up to 336 h (Abraham *et al*., 2019; Taylor and Sethi, 2011; Cuhadar *et al*., 2012), freezing temperature up to 12 weeks, after freezing cycles at -20°C (Taylor and Sethi, 2011) and after temperature fluctuations (Haslacher *et al*., 2017) (Tables 1-5).

Table 1: Stability of different analytes in whole blood

Time (h)	Whole blood Room T°
6	Potassium; amylase; magnesium
10	Phosphate; direct bilirubin; CO_2
24	Creatinine; ALAT; triglyceride; urea; cholesterol; ALP; LDH; ASAT; total bilirubin; GGT; albumin; sodium; HDL; calcium; total protein; creatinine kinase; uric acid; CRP; ferritine; lipase; iron; chloride, transferrin

Table 2: Stability of different analytes in plasma

Time (h)	Plasma Room T°	 4-10°C
6	Albumin; potassium; calcium; total protein; CK; uric acid; CRP; lipase; chloride; transferrin; CO_2	Creatinin; total bilirubine; GGT; albumin; calcium; CK; uric acid; amylase; Magnesium; phosphate; iron; chloride;direct bilirubin; transferrin
12	Creatinin; triglyceride; cholesterol; ALP; LDH; total bilirubin; sodium; calcium; amylase; ferritine; magnesium; phosphate; iron; direct bilirubin; LDL	-
24	Urea; GGT; HDL; glucose	Glucose
48	-	Triglyceride; urea; cholesterol; HDL
72	-	ALP; LDH; sodium; potassium; CRP

Table 3: Stability of different analytes in serum

Time	Serum Room T°	 4-10°C	 - T°
24 h	Ferritine; transferrin	-	-
48 h	-	Uric acid; CRP; ferritine	-
120 h/5 days	Urea; albumin; sodium; potassium; calcium; uric acid; glucose; CRP; phosphate; lipase; iron; chloride; direct bilirubin; CO_2	-	-
1 week	ALAT; cholesterol; total protein; CK	Cholesterol	-
336 h/14 days	-	urea; albumin; sodium; potassium; calcium; total protein; CK; glucose; phosphate; lipase; chloride; CO_2	-
56 days	Triglyceride; ALP; LDH; ASAT; Total bilirubin; GGT; HDL; amylase; LDL	ALAT; ALP; LDH; ASAT; total bilirubin; GGT; HDL; amylase; LDL	LDH; total bilirubin; GGT; HDL; amylase; LDL
12 weeks/3 months	Creatinine	Creatinine	Creatinine; ALAT; triglyceride; urea; cholesterol; ALP; ASAT; albumin; sodium; potassium; calcium; total protein; CK; glucose; phosphate; lipase; chloride; direct bilirubin; CO_2

Table 4: Stability of different analytes in serum after cycles of freezing-thawing

	Serum		
	-20°C	-30°C	-196°C
Cycles	Creatinine; ALAT; triglyceride; urea; cholesterol; ALP; ASAT; total bilirubin; GGT; albumine; sodium; HDL; potassium; calcium; total protein; CK; glucose; magnesium; phosphate; lipase; chloride; direct bilirubin; CO_2	Amylase	CRP

Table 5: Stability of different analytes in serum after temperature fluctuation (-75, -65, -75°C)

Serum	
Temperature fluctuation (-75, -65, -75°C)	ALAT, triglyceride, urea, cholesterol, ALP, LDH, total bilirubin, GGT, albumin, sodium, HDL, potassium, CK, CRP, ferritine, phosphate, lipase, iron, transferrin

Sodium

14 articles study sodium stability in different conditions. Sodium shows some significant variations in whole blood stored at 21°C for 10 h (Henriksen *et al*., 2014) and serum stored at 4°C for 2-4 days (Ng and Yeo, 2013). Studies by Zwart *et al.* (2009); Monneret *et al.* (2016); Dupuy *et al*. (2018b) have shown that sodium was stable in whole blood and plasma up to 24 h at room temperature. Serum was stable up to 120 h at room temperature (Tanner *et al*., 2008; Taylor and Sethi, 2011; Parra-Robert *et al*., 2016), up to 336 h in refrigerated temperatures (Dupuy *et al*., 2018b; Taylor and Sethi, 2011), at -20°C for 12 weeks, after cycles of freezing-thawing at -20°C (Taylor and Sethi, 2011) and after temperature fluctuations (Haslacher *et al*., 2017). In plasma, sodium was stable at room temperature for 12 h (Monneret *et al*., 2016; Stahl and Brandslund, 2005; Leino and Koivula, 2009) and at refrigerated temperatures up to 72 h (Dupuy *et al*., 2018a) (Tables 1-5).

High-Density Lipoprotein (HDL)

13 articles study HDL stability in various storage conditions. HDL shows some fluctuations in whole blood stored at 21°C for 10 h (Henriksen *et al*., 2014) and serum stored at 4°C (collected in plain tubes) and 24°C (collected in SST) for 36 h (Cuhadar *et al*., 2012). We noticed the stability of this parameter in other articles: In whole blood stored at room temperature for 24 h (Dupuy *et al*., 2018b), in plasma stored at room temperature for 24 h and at 4°C for 48 h (Dupuy *et al*., 2018b; Stahl and Brandslund, 2005) and finally in serum stored at room temperature, refrigerated temperature and freezing temperature for up to 56 days (Abraham *et al*., 2019; Taylor and Sethi, 2011; Cuhadar *et al*., 2013; Ng and Yeo, 2013; Parra-Robert *et al*., 2016).

HDL was stable after cycles of freezing-thawing at -20°C and even after temperature fluctuations (Taylor and Sethi, 2011; Cuhadar *et al*., 2013; Haslacher *et al*., 2017) (Tables 1-5).

Potassium

13 articles study potassium stability in different conditions. In 5 articles, potassium was unstable: In whole blood at 21°C for 10 h (Henriksen *et al*., 2014), in plasma stored at 4°C for 12 h (Dupuy *et al*., 2018b), at 8°C for 6 h (Leino and Koivula, 2009) and at 20°C for 12 h (Stahl and Brandslund, 2005). And in serum stored at 15°C for 4 h (Tanner *et al*., 2008).

In other articles it was stable: In whole blood at room temperature for 6 h (Monneret *et al*., 2016), in plasma for 6 h at room temperature (Monneret *et al*., 2016) and at 4°C for 72 h (Dupuy *et al*., 2018a). In serum stored at room temperature for 120 h (Taylor and Sethi, 2011; Parra-Robert *et al*., 2016), at refrigerated temperatures up to 336 h (Taylor and Sethi, 2011; Ng and Yeo, 2013), at -20°C for 12 weeks, after cycles of freezing-thawing at -20°C (Taylor and Sethi, 2011) and after temperature fluctuations (Haslacher *et al*., 2017) (Tables 1-5).

Calcium

13 articles study calcium stability. Calcium was unstable in five articles. In whole blood at 21°C for 10 h (Henriksen *et al*., 2014), in serum stored at 35°C for 24 h (Tanner *et al*., 2008), and after freezing-thawing cycles and temperature fluctuations (Cuhadar *et al*., 2013; Haslacher *et al*., 2017). But in study by Taylor and Sethi (2011) the serum was stable even after cycles of freezing at -20°C. This analyte was also stable in whole blood stored at room temperature up to 24 h (Zwart *et al*., 2009; Monneret *et al*., 2016; Dupuy *et al*., 2018b), in plasma stored at room temperature for 6-12 h and at 8°C for 6 h (Monneret *et al*., 2016; Stahl and Brandslund, 2005; Leino and Koivula, 2009) and in serum stored at room temperature for 120 h (Taylor and Sethi, 2011; Parra-Robert *et al*., 2016), refrigerated for 336 h (Dupuy *et al*., 2018b; Taylor and Sethi, 2011) and at -20°C for 12 weeks (Taylor and Sethi, 2011) (Tables 1-4).

Total Protein

12 articles study total protein stability in different conditions. The total protein shows instability in serum after cycles of freezing-thawing (Cuhadar *et al*., 2013; Haslacher *et al*., 2017), but in serum, it was stable even after cycles of freezing at -20°C (Taylor and Sethi, 2011). This analyte was also stable in whole blood stored at room temperature up to 24 h (Zwart *et al*., 2009; Monneret *et al*., 2016), in plasma stored at room temperature for 6 h (Monneret *et al*., 2016) and in serum at room temperature for 1 week (Abraham *et al*., 2019; Tanner *et al*., 2008; Taylor and Sethi, 2011; Cuhadar *et al*., 2012; Parra-Robert *et al*., 2016), at refrigerated temperature up to 336 h (Abraham *et al*., 2019; Taylor and Sethi, 2011; Cuhadar *et al*., 2012; Ng and Yeo, 2013) and at -20°C for 12 weeks (Taylor and Sethi, 2011) (Tables 1-4).

Creatinine Kinase

12 articles study the creatinine kinase stability: In whole blood at room temperature for up to 24 h (Monneret *et al*., 2016; Dupuy *et al*., 2018b), in plasma stored at room temperature and 8°C for 6 h (Monneret *et al*., 2016; Leino and Koivula, 2009).

Tanner *et al*. (2008); Taylor and Sethi (2011); Cuhadar *et al*. (2012); Parra-Robert *et al*. (2016) concluded that the stability in serum can be maintained up to 1 week at room temperature, at refrigerated temperature up to 336 h (Dupuy *et al*., 2018b, Taylor and Sethi, 2011; Cuhadar *et al*., 2012), at -20°C for 3 months, after cycles of freezing-thawing at -20°C (Taylor and Sethi, 2011; Cuhadar *et al*., 2013) and after temperature fluctuation (Haslacher *et al*., 2017). This

parameter was unstable in whole blood at 21°C for 10 h (Henriksen *et al*., 2014) and in serum at -20, -10, 0, 4, and 25°C (Shimizu and Ichihara, 2019) (Tables 1-5).

Uric Acid

11 articles study the stability of uric acid. The instability was noted in whole blood stored at 21°C for 10 h (Henriksen *et al*., 2014) and in serum stored at Rt and 4°C (Taylor and Sethi, 2011; Cuhadar *et al*., 2012). Also, uric acid shows some fluctuations after cycles of freezing and thawing (Cuhadar *et al*., 2013; Haslacher *et al*., 2017). But in the same conditions, uric acid was stable: In whole blood at room temperature for 24 h (Monneret *et al*., 2016; Dupuy *et al*., 2018b), in serum at room temperature for 120 h (Dupuy *et al*., 2018a) at 4°C for 48 h (Dupuy *et al*., 2018b), and in plasma at room temperature and refrigerated temperature for 6 h (Monneret *et al*., 2016; Leino and Koivula, 2009) (Tables 1-4).

Glucose

10 articles study glucose stability in various conditions. This analyte shows some significant variations under different storage conditions. In whole blood at room temperature for 1 h (Kang *et al*., 2013) and in serum at 15 and 24°C for 8 and 1 h, respectively (Tanner *et al*., 2008; Cuhadar *et al*., 2012). Also in Kang *et al*. (2013) article, glucose was unstable after 3 cycles of freezing-thawing at -196°C.

We notice also that this analyte was stable in plasma stored at room temperature and refrigerated temperature for 24 h (Abraham *et al*., 2019), in serum stored at room temperature for 120 h (Taylor and Sethi, 2011; Parra-Robert *et al*., 2016), in refrigerated temperature for 336 h (Taylor and Sethi, 2011; Ng and Yeo, 2013), in -20°C for up to 3 months and after cycles of freezing-thawing at -20°C (Taylor and Sethi, 2011; Cuhadar *et al*., 2013) (Tables 1-4).

C-reactive Protein (CRP)

10 articles study CRP stability. This parameter was unstable after being storaged at 21°C in whole blood for 10 h (Henriksen *et al*., 2014), but stable in the same conditions for 24 h (Dupuy *et al*., 2018b; Kang *et al*., 2013). CRP was stable in plasma stored at room temperature for 6 h and refrigerated for up to 72 h (Leino and Koivula, 2009; Dupuy *et al*., 2018a). In serum, this analyte was stable at room temperature for 120 h (Abraham *et al*., 2019; Tanner *et al*., 2008; Kang *et al*., 2013; Parra-Robert *et al*., 2016), at refrigerated temperatures up to 48 h (Dupuy *et al*., 2018b; Abraham *et al*., 2019) and after cycles of freezing-thawing at -196°C and temperature fluctuations (Kang *et al*., 2013; Haslacher *et al*., 2017) (Tables 1-5).

Amylase

10 articles study amylase stability. In articles by Henriksen *et al*. (2014); Haslacher *et al*. (2017), we noticed that amylase shows some variations when stored at 21°C for 10 h in whole blood and in serum after fluctuations of -75, -65, and -75°C. This analyte was stable in whole blood at room temperature for 6 h (Monneret *et al*., 2016), in plasma at room temperature for up to 12 h, and at refrigerated temperature for 6 h (No study in this case uses more than 6 h for storage of plasma at refrigerated temperature for amylase) (Monneret *et al*., 2016; Stahl and Brandslund, 2005; Leino and Koivula, 2009) and in serum stored at room temperature, refrigerated and freezing temperatures up to 56 days and even after cycles of freezing-thawing at -30°C (Taylor and Sethi, 2011; Shimizu and Ichihara, 2019; Parra-Robert *et al*., 2016) (Tables 1-4).

Ferritine

9 articles study ferritine stability. We noticed that this parameter was unstable in 2 articles: When stored in serum at 25°C for 24 h (Tanner *et al*., 2008) and in whole blood for 10 h at 21°C (Henriksen *et al*., 2014).

Ferritine was stable in whole blood and plasma stored at room temperature for respectively 24 and 12 h (Zwart *et al*., 2009; Dupuy *et al*., 2018b; Haslacher *et al*., 2017), in serum stored at room temperature for 24 h (Abraham *et al*., 2019), at refrigerated temperatures up to 48 h (Dupuy *et al*., 2018b; Abraham *et al*., 2019) and after temperature fluctuations (-75, -65 and -75°C) (Haslacher *et al*., 2017) (Tables 1-5).

Magnesium

9 articles study magnesium stability. We noted that magnesium was unstable in two articles: In serum at 35°C for 24 h (Tanner *et al*., 2008) and in whole blood at 20-25°C for 24 h (Dupuy *et al*., 2018b). Magnesium was stable in whole blood for 6 h at room temperature (Monneret *et al*., 2016), in plasma stored at room temperature for 12 h and at 8°C for 6 h (No study in this case uses more than 6 h for storage of plasma at refrigerated temperature for Mg^{+2}) (Monneret *et al*., 2016; Stahl and Brandslund, 2005; Leino and Koivula, 2009), in serum stored at room temperature for 120 h (Taylor and Sethi, 2011; Parra-Robert *et al*., 2016), at refrigerated temperature for 336 h, at -20°C for 12 weeks and after cycles of freezing-thawing at -20°C (Taylor and Sethi, 2011) (Tables 1-4).

Phosphate

9 articles study phosphate stability. We noticed that phosphate was unstable in whole blood for 10 h at 21°C (Henriksen *et al*., 2014), In serum at 25 and 8°C for 24 h (Dupuy *et al*., 2018b; Tanner *et al*., 2008), and after fluctuation cycles (-75, -65 and -75°C) (Haslacher *et al*., 2017).

Phosphate was stable in whole blood at room temperature up to 10 h (Henriksen *et al*., 2014; Monneret *et al*., 2016), in serum stored at room temperature for 120 h (Taylor and Sethi, 2011; Parra-Robert *et al*., 2016), between 2 and 10°C for 336 h, at -20°C for 12 weeks and after cycles of freezing at -20°C (Tanner *et al*., 2008) and in plasma at room temperature for up to 12 h and at 8°C for 6 h (no study in this case uses more than 6 h for storage of plasma at refrigerated temperature for phosphate) (Monneret *et al*., 2016; Stahl and Brandslund, 2005) (Leino and Koivula, 2009) (Tables 1-4).

Lipase

8 articles study lipase stability. We noted the stability of this parameter in all conditions: In whole blood stored at room temperature up to 24 h (Monneret *et al*., 2016; Dupuy *et al*., 2018b), in plasma stored at room temperature for 6 h (Monneret *et al*., 2016) and in serum stored at room temperature up to 120 h (Tanner *et al*., 2008; Taylor and Sethi, 2011; Parra-Robert *et al*., 2016), in refrigerated temperature up to 336 h (Dupuy *et al*., 2018b; Taylor and Sethi, 2011), at -20°C for 12 weeks and after freezing cycles at -20°C and temperature fluctuations (-75, -65 and -75°C) (Taylor and Sethi, 2011; Haslacher *et al*., 2017) (Tables 1-5).

Iron

8 articles study iron stability. Iron shows some variations in serum stored at 25°C for 24 h and 35°C for 8 to 24 h (Tanner *et al*., 2008). In Henriksen *et al*. (2014), iron was unstable in whole blood for 10 h at 21°C. This analyte was stable in whole blood at room temperature after storage for 24 h (Zwart *et al*., 2009), in plasma at room temperature up to 12 h and 8°C for 6 h (no study, in this case, uses more than 6 h for storage of plasma at refrigerated temperature for Iron) (Stahl and Brandslund, 2005; Leino and Koivula, 2009) and in serum stored at room temperature for 120 h and after 30 temperature fluctuations (-75, -65 and -75°C) (Haslacher *et al*., 2017; Parra-Robert *et al*., 2016) (Tables 1-5).

Chloride

8 articles study chloride stability. We noted the stability of this parameter in all conditions: In whole blood stored at room temperature up to 24 h (Zwart *et al*., 2009; Monneret *et al*., 2016; Dupuy *et al*., 2018b), in plasma stored at room temperature and 8°C for 6 h (Monneret *et al*., 2016; Leino and Koivula, 2009) and in serum stored at room temperature for 120 h (Taylor and Sethi, 2011; Parra-Robert *et al*., 2016), at refrigerated temperatures up to 336 h (Dupuy *et al*., 2018b; Taylor and Sethi, 2011; Ng and Yeo, 2013), at -20°C for 12 weeks and after cycles of freezing-thawing at -20°C (Tanner *et al*., 2008) (Tables 1-4).

Direct Bilirubin

7 articles study direct bilirubin stability. In all articles we chose, direct bilirubin was stable in different storage conditions: In whole blood at 21°C for 10 h (Henriksen *et al*., 2014), in plasma at room temperature up to 12 h, and at 8°C for 6 h (no study in this case uses more than 6 h for storage of plasma at refrigerated temperature for direct bilirubin) (Stahl and Brandslund, 2005; Leino and Koivula, 2009) and in serum at room temperature up to 120 h (Tanner *et al*., 2008; Parra-Robert *et al*., 2016), at -20°C for 3 months and after cycles of freezing-thawing at -20°C for 10 days (Cuhadar *et al*., 2013) (Tables 1-4).

Transferrin

6 articles study transferrin stability. Transferrin shows instability before centrifugation at 21°C for 10 h (Henriksen *et al*., 2014), but Zwart *et al*. (2009) found this analyte was stable in this condition for 24 h. Also, transferrin was stable in plasma stored at room temperature and 8°C for 6 h (Leino and Koivula, 2009) and in serum stored at room temperature for 24 h and after 30 fluctuations (-75, -65 and -75°C) (Tanner *et al*., 2008; Haslacher *et al*., 2017) (Tables 1-5).

Carbon Dioxide (CO_2)

6 study CO_2 stability. CO_2 was stable in all conditions chosen: In whole blood at room temperature for up to 10 h (Zwart *et al*., 2009; Henriksen *et al*., 2014), in plasma at room temperature for 6 h (Monneret *et al*., 2016) and in serum stored at room temperature for 120 h, between 2 and 10°C for 336 h, at -20°C for 12 weeks and after cycles of freezing at -20°C (Taylor and Sethi, 2011).

CO_2 was unstable before centrifugation at 20-25°C for 12 h (Ng and Yeo, 2013) and in serum after storage at 4°C for 2-4 days (Dupuy *et al*., 2018b) (Tables 1-4).

Low-Density Lipoprotein (LDL)

5 articles study LDL stability. In all the articles we chose, LDL was stable. In plasma stored at room temperature for 12 h (Stahl and Brandslund, 2005) and in serum stored at room temperature, refrigerated temperature, and freezing temperature for up to 56 days (Abraham *et al*., 2019; Shimizu and Ichihara, 2019) (Tables 1-4).

Difference between Collection Tubes

Two articles studied the stability of analytes in two collection tubes: SST, PST, SST II and PST II (Ferrari *et al*., 2020; Shin *et al*., 2021).

The distinction between these two tubes lies in the fact that SST II incorporates a novel gel that surpasses the performance of the current gel used in SST. This enhanced gel establishes a more effective separation between the serum and cellular components of blood while also

accommodating a broader range of centrifugation conditions (Bush *et al*., 2001). The PST, or plasma separation tube, employs a mechanical separator that enables the attainment of higher centrifugation speeds (Shin *et al*., 2021). The PST II is designed to stabilize plasma with barrel-shaped polymer acting as a mechanical separator. During centrifugation, cells descend between the separator and the tube walls, giving plasma with fewer residual cells. Following centrifugation, the polymer reverts to its initial form, effectively separating plasma from the erythrocytes and the buffy coat. This design seeks to enhance plasma stability compared to tubes that use gel separation methods (Bautista Balbás *et al*., 2017).

The results show no difference between these tubes except for ASAT, total bilirubin, direct bilirubin, and calcium, total protein, ferritine, and phosphate (Ferrari *et al*., 2020; Shin *et al*., 2021).

Discussion

To discuss this subject, we will divide it into four components:

- Types of samples
- Types of tubes
- Delays before centrifugation
- Delays after centrifugation

Type of Sample

Different types of samples were chosen in the articles depending on the analytes. Serum, plasma, or whole blood, each of these samples can affect the stability of analytes during transportation or storage. In a research conducted by Monneret *et al.* (2016), all analytes were stable both in whole blood and plasma stored at room temperature for 6 h. Another article by Dupuy *et al*. (2018b) studied the stability of CO_2, LDH, and magnesium in whole blood and serum. Before centrifugation, these analytes were stable at room temperature for up to 24 h, and shows important stability in serum at 4°C.

We also noticed the stability of creatinine, urea, ALP, total bilirubin, Albumin, total protein, lipase, chloride, direct bilirubin, phosphate, and CO_2 in whole blood at room temperature up to 24 h (Zwart *et al*., 2009; Henriksen *et al*., 2014; Dupuy *et al*., 2018b).

Most analytes were stable in plasma at room temperature and at refrigerated temperature, but in serum, the range of temperature chosen was very large and the stability was variable, which is confirmed by what the website of Lapcorp: It's preferred to use the serum for the majority of biochemical analytes.

Type of Blood Collection Tube

A lot of tube collection types exist in the industry. Each one has a different composition that can interact with blood to aliquot serum or plasma fractions (Bowen and Remaley, 2014). The comparison of the two collection tubes PST (PST II) and SST (SST II) shows no difference for the majority of analytes except for total protein, ferritine, phosphate (Ferrari *et al*., 2020), ASAT, total and direct bilirubin and calcium (Shin *et al*., 2021). In studies by Dupuy *et al*. (2018b), Stahl and Brandslund (2005); Leino and Koivula (2009), potassium was unstable in lithium heparin tubes, but showed important stability in SST and PST.

Delay before Centrifugation

Certain analytes may become less stable after an extended contact time betwen serum and plasma with cells (Tanner *et al*., 2008; Oddoze *et al*., 2012).

Zwart *et al*. (2009); Henriksen *et al*. (2014); Monneret *et al*. (2016); Dupuy *et al*. (2018); Kang *et al*. (2013) studied the stability before centrifugation. In two articles, all analytes were stable at room temperature (Zwart *et al*., 2009; Monneret *et al*., 2016). In the other ones, glucose, ASAT, ALAT, GGT, LDH, creatinine kinase, uric acid, amylase, CRP, calcium, cholesterol, triglycerides, HDL, ferritine, transferrin, iron, sodium, potassium, phosphate, CO_2 and magnesium were unstable at room temperature for up to 24 h, at least in one article. This instability can be explained by the presence of this component in the cell, which can leak from it over time. That is why it is important to know each parameter and its stability (Tanner *et al*., 2008; Bush *et al*., 2001).

Delay after Centrifugation

Storing serum or plasma after analysis for a certain time can be done in the laboratory for later analysis. In this context, knowing the stability conditions of analytes is important. According to the reviewed studies, all the analytes studied in plasma were stable except for potassium and ASAT. In serum, ALP, lipase, chloride, direct bilirubin, total bilirubin, LDL, CO_2, triglyceride, cholesterol, total protein, creatinine kinase, CRP, and transferrin were stable at room temperature, refrigerated temperature, and freezing temperature, these data are similar to those found by Chauhan *et al*. (2018); Kughapriya and Elanchezhian, (2019). Kang *et al*. (2013) found that, ASAT, GGT, LDH, creatinine, glucose, and urea were unstable after cycles of freezing-thawing at -196°C. These analytes were stable after cycles of freezing and thawing at -20°C, except for LDH (Taylor and Sethi, 2011; Cuhadar *et al*., 2013). in some articles, we noticed some differences in results; we can find analytes stable after cycles of freezing-thawing at -20°C in one article and unstable in the other, such as ALAT, total bilirubin, total protein, Albumin, and calcium (Taylor and Sethi, 2011; Cuhadar *et al*., 2013).

The stability of the other analytes in serum was variable; this can be explained by the methodology chosen, the

materials, the different ranges of room temperature between laboratories, the calibration of the thermometer used, and other factors that can interfere with and change the stability of analytes such as time, coffee, alcohol, cigarettes, medicine, light, etc., (Ellervik and Vaught, 2015).

Conclusion

In summary, our comparison of two collection tubes, PST (PST II) and SST (SST II), revealed instability in various analytes, including total protein, ferritine, phosphate, ASAT, total and direct bilirubin, and calcium.

Prior to centrifugation, creatinine, urea, ALP, total bilirubin, albumin, total protein, lipase, chloride, direct bilirubin, and phosphate remained stable in whole blood at room temperature for up to 24 h.

In plasma, all analytes studied exhibited stability except for potassium, particularly in lithium heparin tubes and ASAT.

In serum, ALP, lipase, chloride, direct bilirubin, total bilirubin, LDL, CO_2, triglyceride, cholesterol, total protein, creatinine kinase, CRP, and transferrin demonstrated stability at room temperature, refrigerated temperature, and freezing temperature. Conversely, ASAT, GGT, LDH, creatinine, glucose, and urea displayed instability after repeated freezing and thawing cycles at -196°C. However, these analytes remained stable after freezing and thawing cycles at -20°C, except for LDH.

This study combined findings from 20 stability studies to provide comprehensive stability information. It is important to mention that stability might change depending on the chosen methodology.

The review focuses on stability within blood, serum, and plasma, but variations in sample collection methods, anticoagulants, and storage conditions might introduce funding factors influencing stability outcomes.

Some studies may not provide complete data, potentially restricting. The depth of analysis and missing information on storage Temperature, duration, and freeze-thaw cycles may lead to a comprehensive assessment of stability factors.

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Conflict of Interest Disclosure

The authors declare no conflicts of interest regarding this research work. They confirm no financial or personal relationships that could potentially bias the study's design, execution, interpretation, or reporting. This research received no external funding and there are no competing interests that could influence the author's objectivity in conducting and presenting the findings.

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Author's Contributions

Samia El Mahi: Conceived the research idea, conducted the data analysis and drafted the initial manuscript.

Asmae Tantane: Conducted the literature review, contributed to the data interpretation and revised the manuscript critically for important intellectual content.

Sanaa Ait Hamou and Said Oubraim: Provided substantial input in the study designed and contributed to the manuscript's revision and finalization.

Ethics

As no new data contributed by human or animal subjects were collected, there were no ethical considerations directly related to the conduct of this research. In terms of interpreting their data, the authors fulfilled ethical obligations by proper citation and acknowledgment of the sources.

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