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A Systematic Review of Simulation Literature in Blood and Blood Components Supply Chains

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Abstract

This study addresses the critical challenge in blood and blood component management, where uncertainty in demand and supply results in a delicate balance between shortages and waste, especially in developing countries. The lack of these resources can worsen health conditions and lead to loss of life. The objective is to investigate supply chain simulation and optimization methods, focusing on reducing costs and shortages. It is concluded that significant advances are concentrated in the management of the stock of blood products, with a notable gap in the planning of blood collection in blood centers. There is continued interest in whole blood and platelets, with the application of integrated methods and algorithms to improve the management of these resources, particularly in studies of Asian origin. The need for comprehensive investigations into the integral management of the supply chain, including logistical aspects, is highlighted. Although simulation methods have been identified, research suggests the need for detailed studies on the advantages of each method. The study highlights the urgency of exploring and improving collection strategies to optimize the supply of blood and blood components. The contribution lies in identifying the stages of the supply chain and supporting theories that advocate optimization and simulation to reduce costs, scarcity, and waste in this context.

Keywords
Supply chain, Simulation methods, Optimization, Blood and Blood Components.

1. Introduction
Advances in health systems have been notable in several aspects related to patient care and the preservation of life. In recent years, there has been a growing emphasis on the search for comprehensive management, aiming for greater efficiency and effectiveness throughout the healthcare process. (Özener et al. 2019). Among the most important supplies, especially in highly complex care, blood, and blood components stand out, the availability of which crucially depends on voluntary donations.

Management of the blood and blood components supply chain is considered one of the most complex issues in health systems, as it considers uncertainty in the donation process, the perishability of blood and its components, preservation, and distribution conditions (Dehaghani et al. 2021). Despite technological advances and scientific research aimed at finding a chemical product or process that replaces blood and its components, there is still no one effective. (Twumasi and Twumasi 2022).

The blood supply chain encompasses responsibility for all processes of collection, testing, processing, storage, and distribution of blood and its components (red blood cells, leukocytes, platelets, whole blood, frozen blood, and plasma) from the donor to the recipient patient, presenting a type of environment in which uncertainty permeates all aspects of its production process (Abbaspour et al. 2021; Van Sambeeck et al., 2022).

Every day, many patients require transfusions for various reasons such as dialysis patients, cases of trauma and adult and pediatric surgeries, anemia, blood loss, burn patients, and patients with hemophilia, among others. (Shokouhifar et al. 2021; Bhandawat et al. 2022). As there is uncertainty in blood donation, the management of this resource is essential to support various medical procedures and the maintenance of human health and life. (Mousavi 2021; Carvajal-Hernández and Osório-Muriel 2022). Therefore, having the right quantity, at the right time, under ideal conditions underlies the need for managing the blood supply chain.
Given this scenario, one of the areas that has experienced notable progress in health management, especially in recent years, is the design and development of blood and blood product supply chains. These advance aims to improve effectiveness in different types of networks present in this chain, covering public, private and hybrid systems, in addition to direct and reverse chains (Mousavi, 2021), mobile and permanent blood collection centers (Abbaspour et al. 2021), as well as centralized and decentralized networks (Bhandawat et al. 2022).

One way to evaluate complex behavior and evaluate blood supply chain scenarios is using simulation, which makes it possible to solve complex problems, reducing costs and waste (Carvajal-Hernández and Osório-Muriel 2022).

Given the above, the following questions arise:
1) Which stages of the blood and blood components supply chain have been addressed in the literature?
2) What methods have been used to optimize and simulate the blood and blood components supply chain?
In view of the above, the aim of this study is to understand the literature overview on simulation and optimization methods for blood and blood component supply chains.

The organization of this article continues in the subsequent sections, starting with the literature review on the blood and blood components supply chain in Section 2. Then, in Section 3, the methodological characteristics of the research are addressed. The results and discussions are outlined in Section 4. Finally, conclusions are presented in Section 5.

2. Methodology

This research was classified based on Gil (2022), having as its nature basic research, of an exploratory-descriptive nature, with a qualitative approach and as an investigation method the systematic review of the literature following the steps of the Protocol Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), proposed by Moher et al. (2010).

According to Hellweg et al. (2021), literature reviews should be conducted according to a structured approach to ensure study rigor and traceability. Therefore, a systematic literature review, following the PRISMA protocol, was used with the perspective of evaluating a fragment of the literature on simulation in blood and blood component supply chains, as this type of study is important in different contexts to justify the need for new studies on the subject (Moher et al., 2010).

The selection process of articles relating to the topic was based on the PRISMA protocol, as mentioned previously, which provides the generation of scientific knowledge on the topic under investigation due to its Constructivist bias. (Moher et al., 2010). This knowledge makes it possible to expand understanding of the topic of simulation of blood and blood component supply chains, carry out more critical analyzes of the literature, as well as identify possible research gaps.

The PRISMA protocol is operationalized in this research through the following steps: (i) selection of a Bibliographic Portfolio (BP) on simulation of the blood and blood components supply chain; (ii) bibliometric analysis of the selected portfolio; (iii) systemic analysis of BP articles; and (iv) research question and opportunities highlighted based on the knowledge built during the process.

The scientific databases Scopus were considered; Web of Science, PubMed, Lilacs, Periódicos Capes and Scielo. The PB selection process begins with the identification of a set of articles that satisfy the delimitations established by the researchers, defining the search commands (keywords and their combinations).
The search term consists of three parts:

a) the first part guarantees result within the scope of simulation/system dynamics;
b) the second part reduces the search to studies that address logistics and supply chain;
c) the third brings this information to the scope of the blood and blood components supply chain.

The search at the bases took place between September 15 and October 20, 2022.

The process of selecting articles to compose the final PB was carried out using EndNote and Excel software, using the inclusion and exclusion criteria as a basis. The inclusion criteria were defined as: journal articles; peer-reviewed journals; articles in English, Portuguese or Spanish; articles published between 2002 and 2022 (20 years); articles with open access; articles that address simulation in blood and/or blood components supply chains. And the exclusion criteria defined were duplicate articles; articles that do not address simulation methods; articles that address supply chain simulation in a context other than the blood and blood components supply chain; articles published before 2002; articles that do not meet the other inclusion criteria.

The articles resulting from this search were placed in the EndNote software. The resulting 812 articles then passed through the second eligibility filter by reading the titles and abstracts, considering the following exclusion criteria: simulation was used only as a cited word, research does not address the context of the supply chain, dealing with domains other than that of the blood and blood components chain, resulting in 82 texts to be read in full.

Readings of the full text will consider the following exclusion criteria: the simulation was used only in keywords and/or references; the simulation was used as a possibility for future research; simulation was not considered in the blood and blood components supply chain management model; the supply chain was not considered in the simulation model.

In the end, the bibliographic portfolio of this systematic review, illustrated in Table 1, resulted in 52 articles, 26 of which were theoretical and 26 were empirical articles.

Table 1. Bibliographic portfolio

code	Author(s)	Tipo	code	Author(s)	Tipo
997	Twumasi and Twumasi (2022)	Empirical	**568**	Bhandawat et al. (2022)	Theoretical
602	Abbaspour et al. (2021)	Empirical	**566**	Carvajal-Hernández and Osório-Muriel (2022)	Theoretical
601	Behroozi et al. (2021)	Empirical	**853**	Doneda et al. (2021)	Theoretical
598	Shokouhifar et al. (2021)	Empirical	**676**	Mousavi et al. (2021)	Theoretical
565	Shirazi et al. (2021)	Empirical	**673**	Dehghani et al. (2021)	Theoretical
910	Kaya and Ozkok,(2020)	Empirical	**651**	Dehaghani et al. (2021)	Theoretical
630	Khalilpourazari et al., (2020)	Empirical	**982**	Özener et al. (2019)	Theoretical
108	Ahmadimanesh et al. (2020)	Empirical	**574**	Ezugwu et al. (2019)	Theoretical
634	Salehi et al. (2019)	Empirical	**146**	Dutta and Nagurney (2019)	Theoretical
172	Selvakumar et al. (2019)	Empirical	**766**	Özener and Ekici (2018)	Theoretical
1032	Attari and Jami (2018)	Empirical	**610**	Clay et al. (2018)	Theoretical
922	Glasgow et al. (2018)	Empirical	**567**	Eskandari-Khanghahi et al. (2018)	Theoretical
856	Arboleda Zúñiga and Salcedo Moncada (2018)	Empirical	**1161**	Rajendran and Ravindran (2017)	Theoretical
773	Osório et al. (2018)	Empirical	**1114**	Lowalekar and Ravi (2017)	Theoretical
1015	Lowalekar and Ravichandran (2017)	Empirical	**609**	Blake (2017)	Theoretical
597	Ramezanian and Behboodi (2017)	Empirical	**593**	Dillon et al. (2017)	Theoretical
589	Osório et al. (2017)	Empirical	**947**	Wen et al. (2016)	Theoretical
797	Gunpinar and Centeno (2016)	Empirical	**645**	Gunpinar and Centeno (2015)	Theoretical
714	Sahinyazan et al. (2015)	Empirical	**873**	Wang and Ma (2015)	Theoretical
286	Blake et al. (2015)	Empirical	**571**	Duan and Liao (2014)	Theoretical
849	Baesler et al. (2014)	Empirical	**341**	Afshar et al. (2014)	Theoretical

342	Blake and Hardy (2014)	Empirical	**872**	Alfonso et al. (2012)	Theoretical
815	Alfonso et al. (2013)	Empirical	**400**	Zhou et al. (2011)	Theoretical
799	Li and Liao (2012)	Empirical	**779**	Van Dijk et al. (2009)	Theoretical
577	Mustafee et al. (2009)	Empirical	**617**	Hemmelmayr et al. (2009)	Theoretical
700	Haijema et al. (2007)	Empirical	**460**	Rytilä and Spens (2006)	Theoretical

The topic of simulation in the blood and blood components supply chain, despite having a relatively small bibliographic portfolio, has shown an increasing trend over the last 15 years. In 2021, a period in which the world was going through a health crisis because of the Covid-19 pandemic, this theme became even more evident (Figure 1).

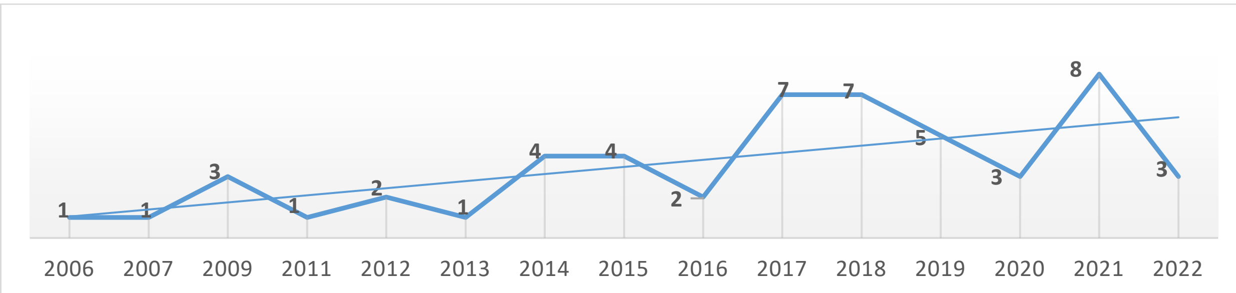

Figure 1. Temporal evolution of the bibliographic portfolio

Evaluating the PB journals (Table 2), the journal "Computers & Operations Research" is the one with the most publications (4 articles), with an impact factor of 5.159 and a percentile of 95%. Among the 11 articles with 2 publications or more, the majority have a percentile above 80%, demonstrating the relevance and impact of research carried out on this topic.

Table 2. Main journals in the bibliographic portfolio on the blood supply chain and blood components

Journal	Percentile	Amount	%
Computers & Operations Research	95%	4	7.69%
Computers & Industrial Engineering	96%	3	5.77%
European Journal of Operational Research	97%	3	5.77%
International Journal of Production Economics	98%	3	5.77%
Transfusion	59%	3	5.77%
Transportation Research Part E: Logistics and Transportation Review	97%	3	5.77%
Annals of Operations Research	82%	2	3.85%
Health Care Management Science	96%	2	3.85%
International Transactions in Operational Research	88%	2	3.85%
Operations Research for Health Care	82%	2	3.85%
Vox Sanguinis	53%	2	3.85%
Journals with just one publication	-	23	44.23%
Total		***52***	***100.00%***

Based on the above, the relevance of the research topic and the interest in high-impact journals for research carried out can be seen. Furthermore, this type of research has social relevance, as it presents methods that aim to optimize blood supply chains and its components, as well as academic relevance, as it presents gaps and opportunities for the development of future research.

3. Results and Discussion

3.1 Characteristics of the bibliographic portfolio of the blood and blood component supply chain

The bibliographic portfolio on the blood and blood components supply chain describes the various stages of the process, starting with the collection of "whole blood", which can later be mechanically separated into different useful components. In this way, a unit of whole blood can be subdivided into five distinct blood products, as shown in Table 3.

Table 3. Description of blood components and useful life

Component	Description	Lifespan
Red blood cells (packed red blood cells)	They are the most abundant cells in the blood and contain a protein called hemoglobin that moves oxygen to our cells.	42 days
Plasma	It is a yellowish liquid component and is obtained by removing red blood cells from whole blood.	1 year
White blood cells	They are part of the immune system and defend the body against infectious agents.	-
Serum	It is a blood plasma without clotting factor, white and red blood cells.	-
Platelets (platelet concentrate)	They can also be taken directly from a person using an apheresis device.	5 days
Cryoprecipitate	Fresh Plasma Frozen at 4°C	1 year

It can be seen in Table 3 that the item with the shortest expiration time and highest probability of shortage is platelets (5 days) and these have been attracting the attention of researchers and managers who aim to reduce waste and increase their bank in order to meet the demands (Shokouhifar et al. 2021).

Blood components are different from blood products, as the first results from the separation through physical processes from whole blood (plasma, red blood cells, leukocytes, platelets, serum), while the second are products obtained on an industrial scale from the fractionation of plasma by physicochemical processes (albumin, immunoglobulins, prothrombin complexes and clotting factors, etc.) (Gunpinar and Centeno 2015).

Blood components can be obtained by collecting whole blood or through apheresis, a method that allows the separation of blood components by centrifugation carried out in automated equipment, allowing the donor's blood to be collected, separating only the platelets, and returning the blood to the body. from the donor through the same venous access (Özener et al. 2019).

Blood and blood supply chain management has high complexity, opening doors for research that point out management methods and tools that will prevent their scarcity.

According to Wang and Ma (2015), there are three typical types of blood scarcity:

a) seasonal blood scarcity that can be caused by the dramatic decline of blood donors for certain periods;
b) Blood structural scarcity that can be caused by insufficient supplies of one or several blood groups; and
c) Regional blood scarcity that can be caused by excessive consumption of blood components in concentrated areas of medical sources.

Blood scarcity usually has a long duration.
Another point pointed out in the literature is cost management, balancing it with other factors. According to Bhandawat et al. (2022), to achieve a balance between costs, product waste and scarcity, any structure used to manage the supply of blood products and blood components must accommodate: (1) a regular supply of blood bank products to hospitals and installations end user during normal operating conditions; (2) rapid transfer of blood from blood bank or other

demand nodes during emergency conditions; and (3) reallocation of excess inventory among us demand to reduce the risk of outdated and scarcity.

Platelet stock has received greater attention in recent years, as it is a blood component with a great complexity in its management, mainly because it has such a short perishable period (Eskandari-Khanghahi et al. 2018). The biggest challenge in blood components' management lies in the uncertainty of demand and blood supply, with a finger-off between scarcity and waste, especially in most developing countries (Carvajal-Hernández and Osório-Muriel 2022).

Most of the literature in the blood supply chain is focused on individual echelons and does not consider relations between the different stages of the supply chain (Osório et al., 2017). Table 4 classifies BP according to the chain steps in: supplies, internal and distribution.

Table 4. Approaches at each stage of the chain by the bibliographic portfolio

	CHAIN STAGE		
	SUPPLIES	**INTERNAL**	**DISTRIBUTION**
PAPERS	997, 602, 108, 634, 922, 856, 773, 1015, 597, 589, 577, 676, 673, 651, 766, 1114, 609, 593, 947, 645, 779, 460	602, 108, 634, 922, 856, 773, 1015, 342, 577, 853, 676, 673, 651, 1114, 593, 873, 341, 872, 779, 617	602, 601, 598, 565, 910, 630, 108, 634, 172, 1032, 922, 856, 773, 1015, 797, 714, 286, 849, 815, 799, 577, 700, 568, 566, 676, 673, 651, 574, 146, 610, 567, 1161, 1114, 593, 571, 400, 779

The product of this most prominent chain is even the blood with just over 48% of the publications, followed by studies with an emphasis on the optimization of platelet supply chains, due to their high degree of perishable, just over 19%. The chain presents the blood components in 5th place with 3.85%. And blood and blood components are analyzed together, being in 3rd place (Figure 2).

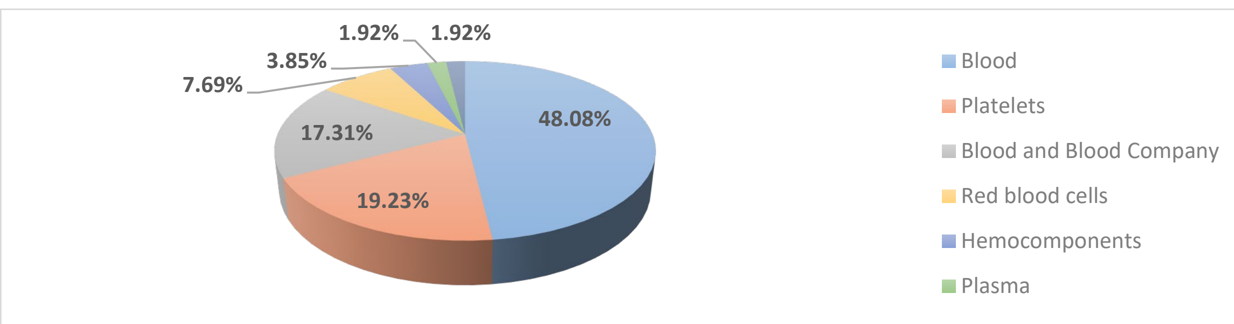

Figure 2. Main products studied in blood supply chains

In addition to the concern for production, packaging and storage, another factor contemplated in the research of recent decades is about writing with a view to reducing not only displacement costs, but also avoiding the lack in one center and excess in another, as well as facilitating redistribution to other centers in the chain (Clay et al. 2016; Hosseinifard and Abbasi, 2018).

Eskandari-Khanghahi et al. (2018) reinforce that minimization of total cost and environmental effects, in addition to maximizing social effects, are considered as the objectives that will boost the increase in the efficiency of the blood component supply network.

3.2 Blood and blood components supply chain

The interest in managing remote blood and blood component supply chains has existed for more than 60 years, when research began that seeks to optimize chains of perishable products through the application of mathematical and computational methods such as queuing theory, Markov chains, statistical analyses, simulation, and optimization (Dillon et al., 2017).

According to Gunpinar and Centeno (2016), the management of the blood components supply chain began with van Zyl (1964) in the 1960s, who dealt with perishable products in his dissertation. After its publication, there was a limited number of publications available, but this has been growing in recent years. The authors Prastacos (1984), Beliën and Forcé (2012) and Osório et al. (2015) are cited as precursors in the development of studies in the area (Gunpinar and Centeno 2016).

The blood banking industry worldwide is a capital-intensive industry in which the main stakeholders, such as blood suppliers and hospitals/medical centers in many countries, are non-profit organizations (Glasgow et al. 2018).

At every stage of the blood supply chain, blood suppliers (blood service organizations) incur high costs associated with collecting whole blood, processing the collected blood, and segregating the components, testing for disease markers, to storing blood bags at the appropriate temperature and ultimately distribution to hospitals and other medical facilities (Gunpinar and Centeno 2016).

Blood cannot be manufactured artificially and the supply depends on voluntary human donors who cannot be easily predicted and around the world there are intensive campaigns to raise awareness of individuals who fit the criteria to be a donor (Van Sambeeck et al. 2022). It is essential in several treatments, as well as can save lives, as the blood transports substances such as nutrients and oxygen to cells and removes waste from cells (Twumasi and Twumasi 2022).

In this way, the management of blood and blood components supply chains has evolved significantly over more than six decades, driven by pioneering research that applies mathematical and computational methods. From the first investigations by van Zyl in the 1960s to the more recent studies by Gunpinar and Centeno (2016), Prastacos et al. (1984), and Osório et al. (2015), we have observed a growing interest and development in this crucial field of health. The unique nature of the blood banking industry, with its stakeholders predominantly made up of non-profit organizations, highlights the importance of efficient management to optimize costs at every stage, from collection to distribution. The crucial reliance on voluntary donors highlights the ongoing need for awareness campaigns to ensure adequate supply. Ultimately, effective management of these supply chains is essential not only to optimize costs, but also to ensure the continued availability of a vital resource that plays a key role in medical treatments and preserving lives.

3.3 Blood supplies chains and optimization and simulation methods

Over the past few decades, a wide range of solution methods has been implemented to improve blood supply chain problems. Twumasi and Twumasi (2022) emphasize in their study that the methods used to manage the blood supply chain are usually categorized in three: simulation (artificial neural network and Monte Carlo method); Optimization (stochastic programming, linear, dynamic, and whole mixed); and temporal series methods (univariate and multivariate moving averages).

The most used techniques according to the authors include:

a) Integer programming: (Bhandawat et al. 2022; Özener et al. 2019; Dutta and Nagurney 2019; Clay et al. 2018; Zhou et al. 2011);
b) Simulation methodology: (Shokouhifar et al. 2021; Glasgow et al. 2018; Osório et al. 2018; Osório et al., 2017; Haijema et al. 2007; Mousavi et al. 2021; Özener et al. 2019; Lowalekar and Ravi 2017; Dillon et al. 2017; Alfonso et al. 2012; Rytilä and Spens 2006; Van Dijk et al. 2009);
c) Systems dynamics: (Attari and Jami 2018; Mustafee et al. 2009; Wen et al. 2016; Wang and Ma, 2015; Afshar et al. 2014; Alfonso et al. 2012; Rytilä and Spens 2006);
d) Mixed integer programming: (Glasgow et al. 2018; Dehghani et al. 2021; Dehaghani et al. 2021).

Several algorithms were pointed out as a mechanism that enable system optimization as a genetic algorithm, evolutionary strength of force pale II (Spea-II), multi-herbal invasive optimization algorithm of optimization algorithm (MOIWO), FR-NSGA-II and and Whale optimization (WOA) algorithm among others. Hosseinifard and Abbasi (2018) point out that there is little research considering the situation of blood service with stochastic replacement.

Some of the most relevant works associated with this review include: Haijema et al. (2007) which applied Markov's dynamic programming and simulation to a real case of a Dutch blood bank. His work has focused on platelet inventory production and management considering only the costs related to platelet production and stock.

Gunpinar and Centeno (2016), which seeks the reduction of waste and scarcity of red blood cell components and platelets of total blood units in a hospital. Both stochastic and deterministic models of entire programming were developed to explicitly consider blood age in stock, uncertain demand, and the proportion of cross compatibility for transfusion.
Ramezanian and Behboodi (2017), which presented in his study different types of modeling of blood supply chains such as simulation, dynamic programming, goal programming and entire programming. In his study, the blood data of a blood supply network in the large urban-rural region of the Midwest Tehran, Iran, for a period of one year, resulting in computational data of the model.

The blood collection problem considering both a fixed location and a mobile blood collection was approached by Alfonso et al. (2013) and by Şahinyazan et al. (2015). The first study used Petri network models to describe various blood collection processes, donor behaviors and human resources requirements, while the second has a heuristic algorithm of entire programming, with a two -stage stochastic model, aiming respectively.

It is clear from the PB analysis that there is a tendency to use “entire programming” in combination with other mathematical and simulation methods, seeking more assertive solutions to the blood supply chain to reduce costs and waste, as well as increasing chain efficiency.

4. Conclusion
This article manages to list and present the main methods of simulation and optimization in blood supply networks and blood components, showing that there has been an increase in the amount of research aimed at reducing costs and scarcity of this resource, as it lacks may incur aggravation. health situation or even fatal loss of lives.

4.1 Theoretical implications
The biggest challenge for blood management and blood components identified in the literature lies in the uncertainty of demand and blood supply, with a trade-off between scarcity and waste, especially in most developing countries. It is also noticed the combination of combined algorithms and combined methods to leverage positive results in managing this feature. There is the concern to involve elements of sustainability (Mousavi 2021), mechanisms for managing these resources in crisis situations, such as earthquakes or natural disasters (Ramezanian and Behboodi, 2017; Salehi et al. 2019; Behroozi et al. 2021).

Most studies are Asian and can encourage Westerners to develop further studies, considering all stages of the supply chain and contemplating the logistical processes in their fullness. Among the blood components, there is still a strong interest in “total blood” and the “platelets” component, both to meet a larger core and to treat the complexity of the blood and this blood component.

Thus, based on the above, it is possible to state that most of the advances mentioned in the articles that make up this bibliographic research portfolio focused on blood product management. Therefore, there is scarce literature on the planning of the blood collection process of the blood centers.

4.2 Future Limitations and Research
This research focuses on identifying simulation methods, but the analysis of the specific steps of the supply chain addressed in the studies is limited, questioning where they are concentrated. However, as a proposal for future studies, a deeper approach is suggested, detailing each method and its advantages over the others. This would allow a more complete and refined understanding of simulation strategies in blood supply chain management and blood components.

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