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Designing an integrated blood plasma supply chain under uncertainty demand of both therapy and medicine

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Abstract

Blood plasma is a yellowish liquid component of blood that holds the blood cells (red blood cells, white blood cells, and platelets) in whole blood in suspension. Plasma is human-based so that it just makes in the body thus only donors can be the source for preparing plasma. Plasma has usage in two-part therapy and medicine. This article addresses the design of an integrated blood plasma supply chain network considering demand in two segments of therapy and medicine. To this goal, a MILP scenario-based mathematical programming model is developed which minimizes the total cost as well as the unsatisfied demand. After that, the actual data of a case study are used to illustrate the applicability also the performance of the offered model as well as validation. The obtained results show the superiority of the recovered plasma method compared to the apheresis plasma method for the blood transmission network. As well, the maximum use of the capacity instantly after the opening of each collection centers is beneficial for reducing the total cost.

Keywords: Blood plasma supply chain, network design, health systems, scenario-based optimization

1-Introduction

Whole blood (WB) includes two general sections; a cellular part, and a liquid part. The cellular part includes three components red blood cells, white blood cells, and platelets. Besides, the liquid part is called plasma that it is yellow and water-filled. Also, all blood cells components are suspended in it. Plasma (PLS) includes proteins, nutrients, gases, wastes, and hormones that are used for producing plasma drugs (Feher, 2012).

PLS makes only in the human body. Therefore, just donors can be a PLS source. PLS, as an important hematic product, is widely used in the national healthcare networks of countries. Although, for its long-lived, some know it just an imperishable part of WB and less important (Prastacos, 1984).

PLS has usage in two-part therapy and medicine. PLS donated is using directly for therapy additionally it is converting to drugs and is consumed indirectly. More than the therapeutic aspect, the segment of PLS medicine is highly important because the raw material their production just provide through human plasma. PLS drugs are expensive and rare because there are not good alternatives for plasma-derived medicinal products (PDMPs).

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Moreover, according to the instructions of the World Health Organization, to prevent the disease outbreaks of regional and geographic (as were happening about human coronavirus disease (COVID-19) in first quarter 2020), each area should use the plasma collected from the same area for its plasma needs. So, if each country uses its people plasma, it will be more inexpensive and safer for its health network.

PLSs play a role in therapy Immunodeficiency diseases, Hemophilia, Severe burns, and Multiple sclerosis (Rytile and Spens, 2006). In the medicine segment, there are numerous PDMPs, but the three main ones are human albumin solution, coagulation factors (e.g., Factor VIII, Factor IX), and immune globulin intravenous.

Under the previous material, the necessity of designing an integrated supply chain for plasma is taken into consideration by the national healthcare networks of countries. This paper presents an integrated blood plasma supply chain for answering the demand differentiated in the therapy and medicine part.
The Blood Plasma Supply Chain (BPSC) includes the process of collecting both WB and PLS from donors, testing, producing, and finally distributing PLSs and PDMPs to Health Centers (HCs) and pharmacies. The uncertainty in the supply and demand points and wastage of PLSs in the therapy side as well as the shortage of PLSs in the medicine side, are three major factors that complicate BPSC. The main challenge in BPSC is permanent access to the continuous donors for better management of the supply side, reduce wastage the PLSs of the segment of therapy and compensate shortage the PDMPs segment of medicine. According to the World Health Organization report, 87.5 % of developing countries collected less than half of the WB needed (WHO, 2010). Also, during the years 2012, 2013, and 2014 respectively was recorded as 30.1%, 26.4% and 23.4% of the blood wasted was recorded (Kurup *et al.*, 2016). One unit of PLS is consumed for every 5 units of packed red blood cells transfused, as a result, four-fifths of the PLS produced in the world is wasted. It is estimated that in developing countries 9.5 million liters of PLS are lost annually while it can be converted to PDMPs.

In most countries, generally, there are two types of PLS donation: the Apheresis Plasma (AP) that PLS can be drawn directly from a donor, also the Recovered Plasma (RP) that PLS is separated from the donated WB (Liu *et al.*, 2016). In method AP (also known as the source plasma or automated apheresis), same as Platelets (PLTs), the WB withdrawn from one hand of a donor (e.g. right hand), PLS separated from the WB and the remaining WB returned without PLS will back into the donor's body, through the other hand (e.g. left hand) (figure 1) (Simon, 1994).

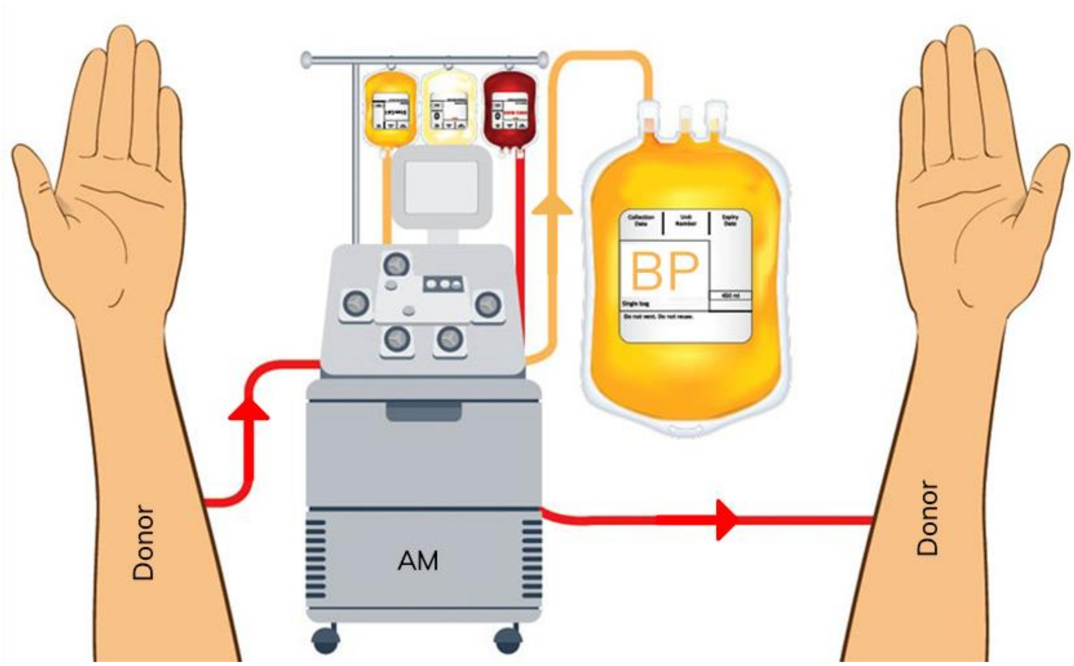

Fig 1. Apheresis process

In method RP, the PLS will separate through centrifugal force from the cells of WB donated by a centrifuge machine as shown in figure 2 (Burnouf *et al.*, 2007).

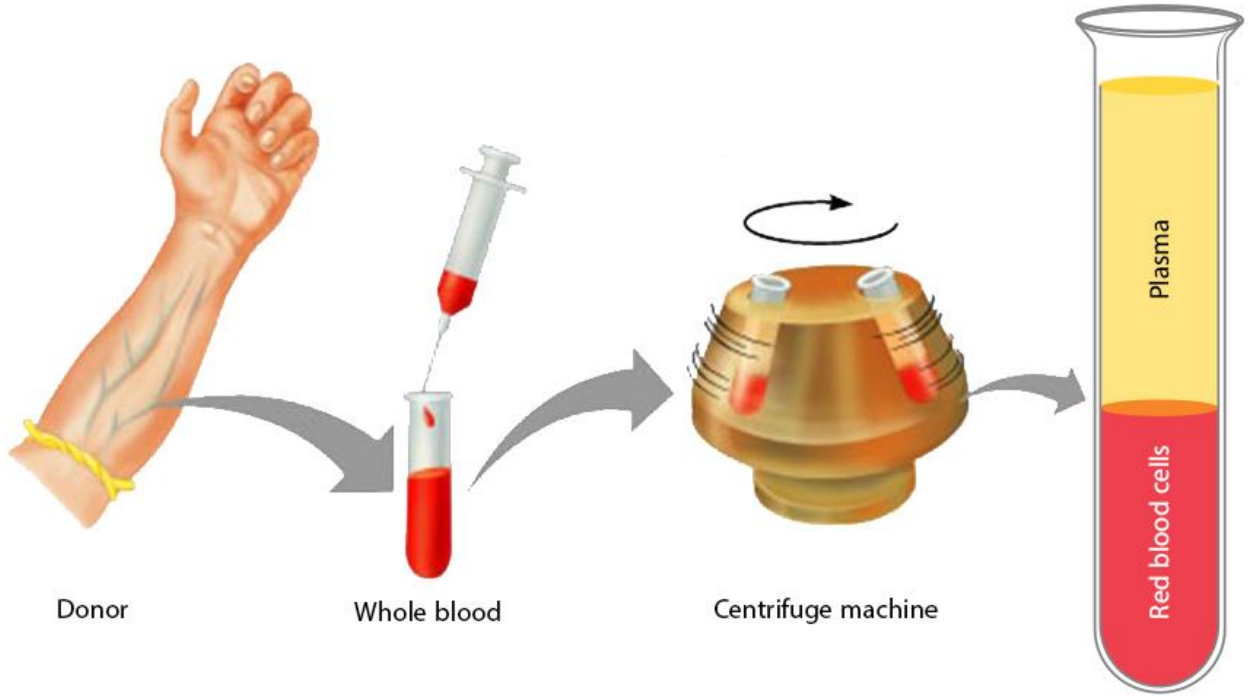

Fig 2. Recovered process

In way of AP, the PLSs about two times more than RP can be extracted. In the AP way, the authorized volume ranges in each the donation is between 400 and 800 ml and for RP way, it ranges between 450 and 500 ml, without included of the anticoagulant (Laub *et al.*, 2010) and (Burnouf *et al.*, 2007). Besides the PLS collected by APs are better than the PLS separated RPs for converting to PDMPs however the infrastructure needed for the collection of the AP is very expensive. The researches show the quality of PLSs collected by AP is higher than RP from WB. Specifically, AP contains substantially greater coagulation factors than RP (Runkel *et al.*, 2005) and (Bult, 2011).

Mathematics and optimization approaches can assist blood transfusion network to overcome the complexity of BPSC, ranging from donor management in Collection Centers (CCs) to the wastage management of PLS in health centers (HCs). The BPSC is including collecting, processing, and distributing. In this paper, we consider an integrated BPSC addressing several CCs, a single regional Blood Transfusion Center (BTC), several HCs (e.g., hospitals), also one Provision Center (PC) (figure 3).

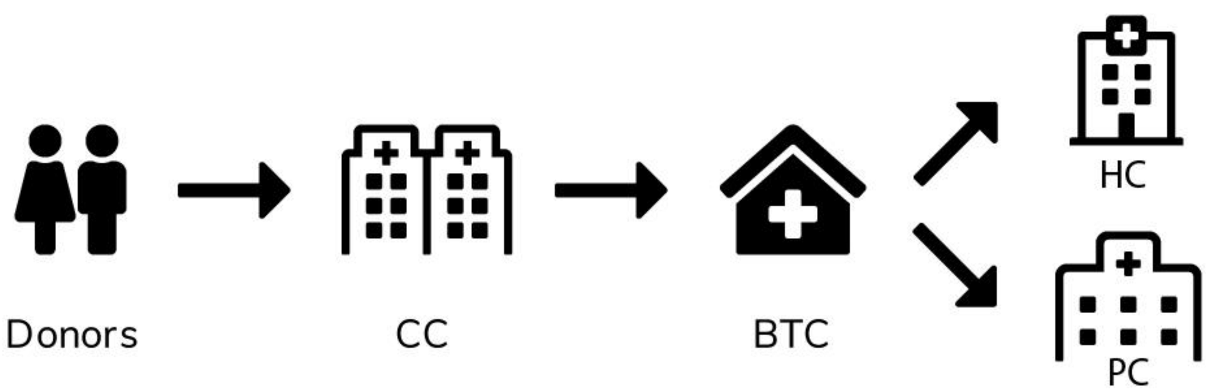

Fig 3. Blood plasma supply chain network

2-Literature review

In this segment, at first, some of the studies on planning models for blood supply chain are reviewed then the related articles on blood components supply chain are surveyed. In the end, was surveyed the reviewed articles.

Pierskalla (2005) provided a comprehensive overview in that some decisions of the blood supply chain including WB collection, BPs production, and control of inventory in both tactical and operational levels are covered (Pierskalla, 2006). Jabbarzadeh et al. (2014) proposed a robust optimization model for an emergency blood supply chain facing supply and demand uncertainties at the time of the disasters. This scenario-based model covered both the location of blood facilities (permanent and temporary) and allocation decisions (Jabbarzadeh, Fahimnia and Seuring, 2014). Ramezanian et al. (2017) addressed a mixed-integer linear programming model for the blood supply chain containing the zones of blood donors, the blood facilities (fixed and mobile) and the blood center. The presented model minimizes the supply chain costs including the transportation cost and the cost of movement of temporary facilities (Ramezanian and Behboodi, 2017). Masoumi et al. (2017) developed a methodological framework that compares pre-merger and post-merger models of the blood banks in terms of optimization (Masoumi, Yu and Nagurney, 2017).

Usually use fixed lifetime models for solving problems of perishable blood components in blood banking and inventory (Nahmias, 1982). Cheraghi and Hosseini-Motlagh (2018) proposed a robust stochastic programming model that including a set of disaster scenarios for managing the red blood supply chain, without considering of disruptions in the fixed blood center and the laboratories (Cheraghi and Hosseini-Motlagh, 2018). Jafarkhan and Yaghoubi (2018) formulated a flexible and robust inventory-routing problem of the red blood supply chain under uncertain for fast responsibility of shortage. The scenario-based model minimized the total cost containing conduction, replacement, and inventory (Jafarkhan and Yaghoubi, 2018). Ensafian and Yaghoubi (2017) considered an integrated PLT supply chain that includes procurement, production, and distribution with the ultimate goal of increasing service quality and effective treatment of patients. The model was written according to three types of platelets that categorized by their age, Fresh, Young, and Old were considered respectively 1 day, old 2–3 days old, and 4–6 days old (Ensafian and Yaghoubi, 2017). Ensafian et al (2017) developed an integrated multiperiod mixed-integer scenario-based two-stage stochastic programming model focusing on tactical and operational decisions with considering the ABO-Rh compatibility priority and PLT age groups (Ensafian, Yaghoubi and Modarres Yazdi, 2017). Yaghoubi and Kamvar (2017) offered a math model for PLT supply chain that while decreasing the cost of system logistical and retain the freshness of PLT additionally added the possibility of lateral transshipment of PLT between the hospitals for increasing the speed of answer to demand uncertainty (Yaghoubi and Kamvar, 2017). Gilani Larimi and Yaghoubi (2019) suggested a novel model for PLT supply chain with two aims the decreased in the under fulfilled demand and the optimized total costs. Besides, the model divided PLTs into three different ages and also checked in a practical real case study (Gilani Larimi and Yaghoubi, 2019). Gilani Larimi et al (2019) addressed an itemized blood supply chain for PLT that have unidirectional lateral transshipment from hospitals to health center for answering to the PLT shortage for three different types of patient (Gilani Larimi, Yaghoubi and Hosseini-Motlagh, 2019). Yaghoubi et al (2019) offered a novel integrated bi-objective multi-product model while considering demand uncertainty and facility disruption simultaneously. Their model in addition to consideration three different PLT, investigated a real-world case study to manage the PLT supply chain network (Yaghoubi *et al.*, 2019).

Furthermore, in the past few years, four survey articles in the field of the blood supply chain provided a comprehensive review to support researchers in this string whose aim is to identify its main challenging problems. As displayed in Fig 4, the average percentage of the blood articles during the fields red blood cell, WB, PLT, and PLS was recorded as 37%, 31%, 26%, and 7%, respectively. According to the survey articles, has not any attention to the medicine part. Besides, the papers that paid about plasma in the therapy segment had less consideration of the dedicated plasma features, especially in the collection, separation, production, and distribution parts. Additionally, Beliën and Forcé (Beliën and Forcé, 2012) surveyed the blood articles since 1966 up to 2011, Jafari, Kianfar and Moayer (Jafari, Kianfar and

Moayer, 2016) developed it up to 2014, Osorio, Brailsford and Smith (Osorio, Brailsford and Smith, 2015) added 2015`s articles, Vanany and Indah Arvitrida (Mansur, Vanany and Indah Arvitrida, 2018) extended it up to 2017, and this paper completed it up to 2019.

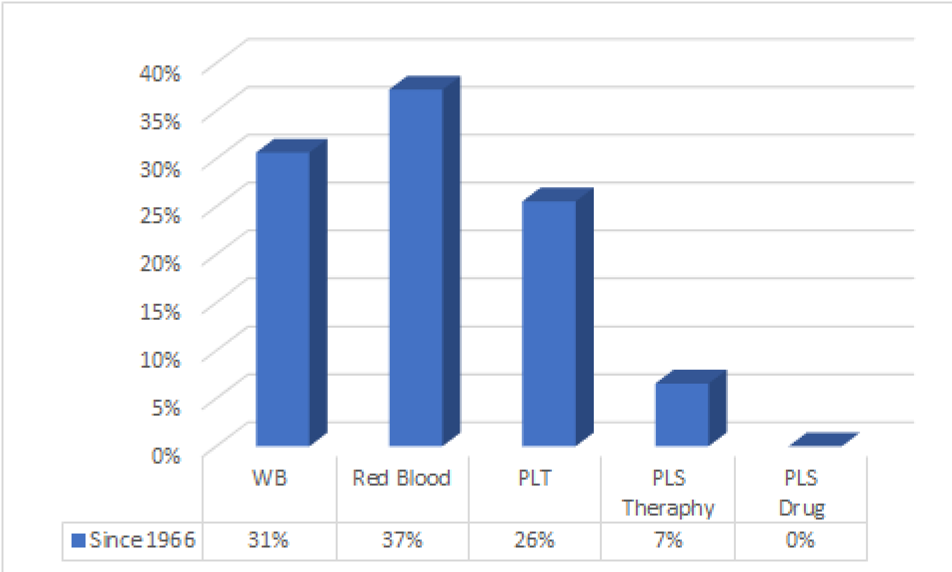

Fig 4. The blood articles categorized by blood components since 1966

The motivation for this study is to optimize all BPSC stages to achieve cheaper PDMPs by patients and to decrease the wastage of PLSs. The main contributions that differentiate this research from other studies are the following:

- Attention to both usage of PLS (medicine and therapy).
- Both AP and RP collection ways (as two common types of PLS collection methods) were considered in the integer programming model.
- Offered the novel approach to tackle with intrinsic uncertainty in the demand side is proposed as a scenario-based optimization programming model.
- For showing the practicability of the presented application, the suggested model is performed in a real case study.

3-Problem definition and mathematical formulation

In the real world, the donation units of blood at CCs are sent to the BTC for the production of blood components. The donated WB units must be transferred to the BTC within less six hours otherwise, they cannot be used for the blood components production (Mobasher, Ekici and Özener, 2015). The blood components are processed at the BTC then delivered to with the priority to HCs and the second priority to PC based on their demand. In this study, motivated by the gap found in the literature, the model was formulated to be accountable to both the PLS demands (therapy and medicine) with the least shortage.

The supply chain under investigation consisted of several CC facilities, the BTC, the several HCs, and the PC. The blood components are processed at the BTC and converted to fresh frozen plasma. At first, the fresh frozen plasma sent to HCs for satisfying the therapy demand, so shortage is not allowed the segment. In the second step, the surplus fresh frozen plasma is sent to PC for satisfying the medicine demand, however, the shortage is allowed in this part. The deficiency of PLS in the second part can be purchased from abroad. Therefore, the article model considers an integrated blood supply chain including all stages of the collection, the production, and the distribution of PLS.

The proposed model determines the optimal number of WB and PLS units required, the optimal amount of production of PLS, assignment of PLS units to each HCs, and the assignment of PLS units to the PC to minimize the total cost in one year.

In this study, the following assumptions have been considered:

- The count of the donation of the donors, both AP and RP way, is limited for each region.
- The capacity for the collection of PLSs from WB at CCs is limited.
- The capacity for the collection of PLSs in way of AP at CCs is limited.
- The capacity for production (separation) of PLS from WB at BTC is unlimited.
- In the therapy segment, the PLS shortage for HCs is not admissible.
- In the medicine segment, a shortage cost is incurred when a demand is not satisfied in PC.

3-1-Notation

The following notations are used in the proposed mathematical programming:

Sets

I	Index of donor regions, $i = 1, \ldots, I$
J	Index of candidate locations for CCs, $j = 1, \ldots, J$
K	Index of BTC, $k = 1$
H	Index of HCs, $h = 1, \ldots, H$
P	Index of PC, $P = 1$
S	Index of demand scenario, $s = 1, \ldots, S$
Parameters	
$CL(j)$	Cost of locating a CC facility in the candidate location j
$CD(j,k)$	Cost of delivering a PLS or a WB pack from a CC facility located at j to the BTC k
$CSP(k)$	Cost of separating each liter of PLS from WB at the BTC k
$CPP(k)$	Cost of producing each liter of PLS at the BTC k
$CDH(k,h)$	Cost of delivering each liter of PLS from the BTC k to a HC h
$CDP(k,p)$	Cost of delivering each liter of PLS from the BTC k to the PC p
$CBP(p)$	Cost of buying each liter of PLS from abroad to the PC p
$CapP(j)$	Capacity of PLS at a CC facility j
$CapW(j)$	Capacity of WB at a CC facility j
$PS(s)$	Probability of occurrence of scenario s
$DH^s(h)$	PLS Demand of a HC h under scenario s
$DP^s(p)$	PLS Demand of the PC p under scenario s
$MW(i)$	Maximum times that donors can donate WB in region i
$MP(i)$	Maximum times that donors can donate PLS in region i
$AP(k)$	Average PLS that any donors can donate at CC in each time
$AW(k)$	Average PLS that the BTC can separate from any WB bag
M	A reasonably large number
Variables	
$AsP^s(i,j)$	1 if region i of donors is assigned to a CC facility j for PLS donation under scenario s 0 otherwise
$AsW^s(i,j)$	1 if region i of donors is assigned to a CC facility j for WB donation under scenario s 0 otherwise
$Z(j)$	1 if a CC facility is opened in location j 0 otherwise
$NW^s(i,j)$	Number of donors of region i that donate WB in CC facility j under scenario s
$NP^s(i,j)$	Number of donors of region i that donate PLS in CC facility j under scenario s
$NPD^s(j,k)$	Number of PLS bags delivered from CC facility j to the BTC k under scenario s
$NWD^s(j,k)$	Number of WB bags delivered from CC facility j to the BTC k under scenario s
$VPH^s(k,h)$	The PLS volume delivered from the BTC k to a HC h under scenario s

$VPP^s(k,p)$	The PLS volume delivered from the BTC k to the PC p under scenario s
$VSP^s(p)$	The PLS volume shortage of demand of the PC p that should buy from abroad under scenario s

3-2-Model: Mixed-integer programming

This section presents the mixed integer model:

$$\begin{aligned} Min\, Z = \sum_j Z(j) \times CL(j) & \\ + \sum_s PS(s) \times (\sum_{j,k} CD(j,k) \times \left(NWD^s(j,k) + NPD^s(j,k)\right) & \\ + \sum_{j,k} NWD^s(j,k) \times AW(k) \times CSP(k) & \\ + \sum_{j,k} NPD^s(j,k) \times AP(k) \times CPP(k) + \sum_{k,h} CDH(k,h) \times VPH^s(k,h) & \\ + \sum_{k,p} CDP(k,p) \times VPP^s(k,p) + \sum_p CBP(p) \times VSP^s(p)) & \end{aligned} \tag{1}$$

Subject to:

$$AsW^s(i,j) \le Z(j) \qquad \forall i,j,s \tag{2}$$

$$AsP^s(i,j) \le Z(j) \qquad \forall i,j,s \tag{3}$$

$$\sum_j AsP^s(i,j) + \sum_j AsW^s(i,j) \le 1 \qquad \forall i,s \tag{4}$$

$$NW^s(i,j) \le M \times AsW^s(i,j) \qquad \forall i,j,s \tag{5}$$

$$NP^s(i,j) \le M \times AsP^s(i,j) \qquad \forall i,j,s \tag{6}$$

$$\sum_j NW^s(i,j) \le MW(i) \qquad \forall i,s \tag{7}$$

$$\sum_j NP^s(i,j) \le MP(i) \qquad \forall i,s \tag{8}$$

$$\sum_j NW^s(i,j) \le CapW(j) \qquad \forall i,s \tag{9}$$

$$\sum_j NP^s(i,j) \le CapP(j) \qquad \forall i,s \tag{10}$$

$$\sum_i NW^s(i,j) = \sum_k NWD^s(j,k) \qquad \forall j,s \tag{11}$$

$$\sum_i NP^s(i,j) = \sum_k NPD^s(j,k) \qquad \forall j,s \tag{12}$$

$$\begin{aligned} \sum_j NWD^s(j,k) \times AW(k) + \sum_j NPD^s(j,k) \times AP(k) = \sum_h VPH^s(k,h) & \\ + \sum_p VPP^s(k,p) & \end{aligned} \qquad \forall k,s \tag{13}$$

$$DH^s(h) = \sum_k VPH^s(k,h) \qquad \forall h,s \tag{14}$$

$$DP^s(p) \le \sum_k VPP^s(k,p) + VSP^s(p) \qquad \forall p,s \tag{15}$$

$$AsP^s(i,j), AsW^s(i,j), and\ Z(j) \in \{0,1\} \qquad \forall i,j,s \tag{16}$$

$$NW^s(i,j), NP^s(i,j), NPD^s(j,k), NWD^s(j,k), VPH^s(k,h), VPP^s(k,p), \text{ and } VSP^s(p) \geq 0 \qquad \forall i,j,k,h,p,s \quad (17)$$

The total cost is minimized under each scenario in equation (1). This cost includes the opening of CCs, the collection of both WB and PLS, the producing of PLS, the separation of PLS from WB, the transportation of WB and PLS bags from the CCs to the BTC, the shipping of PLS bags from the BTC to the HCs and the PC, and the shortage in the PC.

All of the constraints (4 to 15) must be available under each scenario.

Constraints (2) and (3) warrant that a donor (for donation WB or PLS) can only be assigned to a CC facility if it has already been opened. In each time, it is assumed that every group of donors can donate just to either the AP or the RP way (not to both methods simultaneous) that is assured via constraints (4). Constraints (5) and (6) guarantee that donors (for donation WB or PLS) assigned to a CC if the CC has been established in relevant candidate locations. Constraint set (7) and (8) define the maximum times that donors can donate in AP or RP way. Moreover, constraint (9) and (10) ensure that the inventory of WB (or PLS) units at the CC does not exceed the capacity of the WB (or PLS). Equations (11) and (12) assure that the total bags of collected WB (or PLS) by each CC should be delivered to the BTC. Constraint (13) is the balance equation that shows the total bags of collected PLS plus the total PLS separated from WB by the BTC should be delivered to the HCs and the PC. Constraint (14) designates the uncertainty demand of each HC under each scenario. Additionally, this constraint says the PLS shortage not allowed for any HC. Constraint (15) indicates the uncertainty demand of the PC under each scenario. However, this constraint represents the PLS shortage is allowed for the medicine segment. Finally, constraints (16) and (17) describe the type of decision variables, binary and positive respectively. This model is linear so it solved with the GAMS software in a reasonable time without a solution approach.

4-Case study

The world's blood donation figures were about 177 million units last year (2019) that Iran's share was 2 million and 5,000 units. According to the Melbourne Declaration of the World Health Organization, access to all blood resources through voluntary non-material donors for all countries is planned and envisaged by year 2020. However, since the year 2007, Iran has been able to achieve 100% voluntary blood donation. In the report of the Iranian Blood Transfusion Organization bring that in Iran per 1000 population there are 27 donors while they donate WB, PLT, and PLS. At the moment (2019), about 60% of blood donors in Iran donate regularly (with a history of blood donation at least 2 times a year), 28% have once previous experience with blood donation, and 12% donate first-time (Gharehbaghian, Abolghasemi and Namini, 2008).

Tehran is the most populous city also is the capital of Iran. The utmost of the blood donation (WB and blood components) is often in Tehran, nearly 24% of the total country. Additionally, the most consumable blood occurs in Tehran, almost 27% of the total country.

Tehran has 5 candidate locations for the opening of the CCs, one BTC, and 10 major public therapeutic centers which mainly provide health services for patients Immunodeficiency diseases, Hemophilia, Severe burns, and Multiple sclerosis. Also, it has one PC. For this survey, the required data was gathered from activists working in the PLS medicine segment in Tehran. Moreover, the valuable data was prepared from activists working in the PLS therapy segment in all three sections academic, education, and operation in Tehran. The metropolis of Tehran is divided into 22 municipal districts, each with its administrative center. 20 of the 22 municipal districts are located in Tehran County's Central District, while the districts 1 and 20 are respectively located in the counties of Shemiranat and Ray. Although administratively separate, the cities of Ray and Shemiran are often considered part of Great Tehran. The geographical location of the CCs (candidate locations), the BTC, the PC, and the HCs are marked out in figure 5.

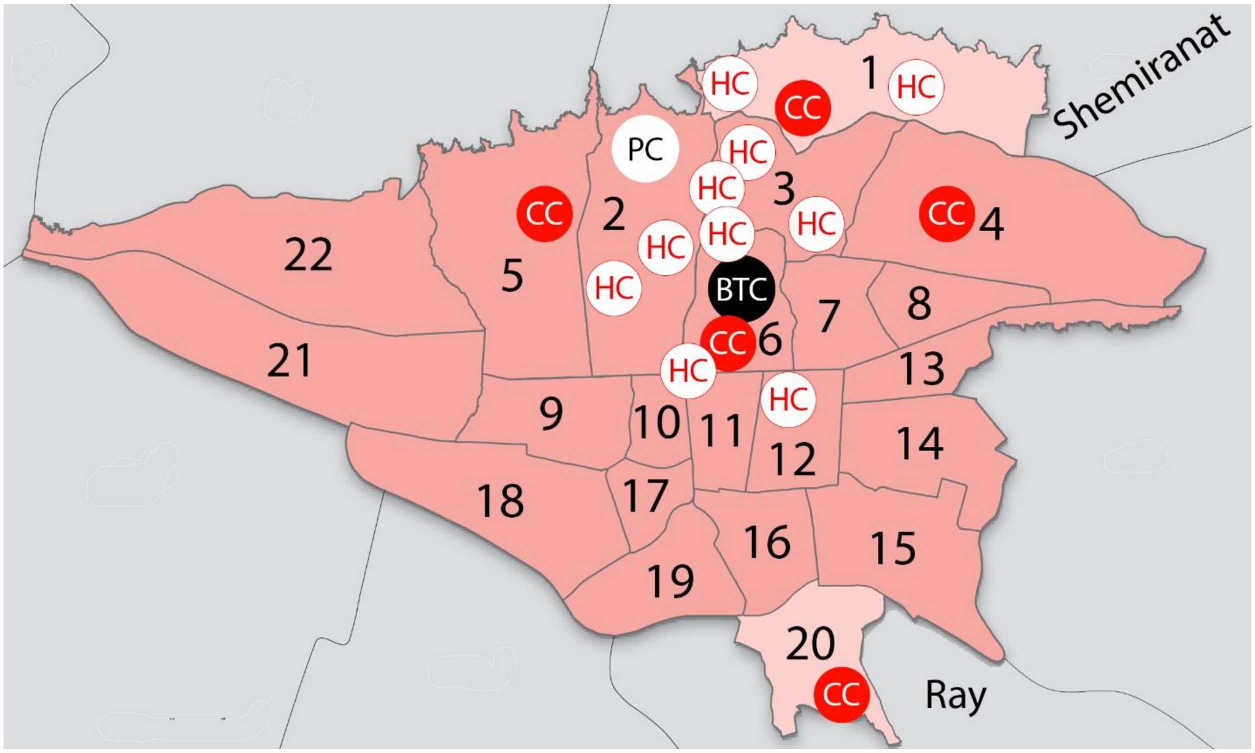

Fig 5. The geographical location of facilities in Tehran

In this section, the article model tested with data of the real case, and its results are analyzed. At first, we solve the deterministic model without any scenario. Afterward, the uncertainty demand of both therapy and medicine will be added to the model in the form of three types of scenario optimistic, pessimistic, and realistic. The coding of the present study was performed by GAMS 27.3.0 using CPLEX solver on a Sony Vaio laptop (F VPCF11KFX/H) with 1.6GHz Intel Core i7-720QM Quad-Core CPU and 4GB (2x2GB) RAM. The parameters used in the proposed Mixed-integer programming are summarized in Table 1 while the demand for therapy and medicine under each scenario can be seen in table 2 and table 3.

Table 1. Parameter data setting

Parameter	Value	Unit
Cost of locating CC	Uniform (3,227,778-3,945,062)	$
Cost of delivering	Uniform (0.1-0.2) (Ensafian and Yaghoubi, 2017; Ensafian, Yaghoubi and Modarres Yazdi, 2017)	$ per bag
Cost of separation WB	119 (Eandi *et al.*, 2015)	$ per liter
Cost of production PLS	206 (Eandi *et al.*, 2015)	$ per liter
Cost of buying PLS	300	$ per liter
Capacity of AP way	Uniform (90,000-110,000)	Bag (Donor)
Capacity of RP way	Uniform (131,400-160,600)	Bag (Donor)
Maximum WB donation	Uniform (43,636-53,333)	Bag (Donor)
Maximum PLS donation	Uniform (8,836-10,800)	Bag (Donor)
Average PLS donation	Uniform (0.500-0.600) (Burnouf *et al.*, 2007)	Liter per donor
Average PLS separation	Uniform (0.180-0.220) (Burnouf *et al.*, 2007)	Liter per donor
M	Uniform (13,100,000-16,100,000)	-

Table 2. Demand of PLS in therapy under three different scenarios

Hospital		Without scenario (Liter) (Oveysi Nejad, 2018)	Scenario (Liter)		
Number	Name		Pessimistic PS=25%	Realistic PS=55%	Optimistic PS=20%
1	Imam Khomeini	6,592	8,570	7,910	7,251
2	Shariati	5,656	7,353	6,787	6,222
3	Milad	5,838	7,589	7,006	6,422
4	Taleqani	5,785	7,521	6,942	6,364
5	Mofid	5,790	7,527	6,948	6,369
6	Motahari	7,516	9,771	9,019	8,268
7	Imam Hossein	5,767	7,497	6,920	6,344
8	Rasoul Akram	5,700	7,410	6,840	6,270
9	Chamran	5,729	7,448	6,875	6,302
10	Sina	5,765	7,495	6,918	6,342

Table 3. Demand of PLS in medicine based on three different scenarios

Scenario	PC (Liter)
Without scenario	Uniform (145,800-178,200)
Pessimistic (PS=25%)	Uniform (230,850-282,150)
Realistic (PS=55%)	Uniform (182,250-222,750)
Optimistic (PS=20%)	Uniform (157,950-193,050)

4-1-Results

In this section, the numerical results obtained based on the real case described in the previous section are presented and the applicability of the proposed model is investigated. The proposed model is firstly solved deterministically and the numerical results are discussed, then demands added to the model considering scenario-based. Table 4 shows a summary of the obtained results for the main variables including the Objective Function (OF) without any scenario. The total number of PLSs delivered to HCs is presented in table 5. As expected, the total demands of the HCs have been delivered, because the shortage is not allowed in this segment. Nonetheless, part of medicine demand has a shortage.

Table 4. The results summary without scenario

Variables	Result
Number of opened facilities	3
The PLS volume shortage	53,929 Liters
The total cost	51,118,152 $

As shown in table 4 the total unmet demand for the medicine segment is 53,929 Liter per year. According to the Iranian Blood Transfusion Organization, in Tehran, there is nearly 54,000 liters of the PLS as a shortage for converting to PDMPs yearly. So, the article model could estimate this shortage with approximation 0%. To meet approximately 100% of the total 60,138 Liters PLSs needed in all the HCs, also 63.94% of the total 149,565 Liters PLSs needed in the PC, 227,922 Liters of WB should be separated, and 131,240 Liters PLS in AP way in the BTC should be prepared.

Table 5. The PLS volume delivered from the BTC to each HC

Hospital No.	1	2	3	4	5
$\boldsymbol{VPH}$ (Liter)	6,592	5,656	5,838	5,785	5,790
Hospital No.	**6**	**7**	**8**	**9**	**10**
$\boldsymbol{VPH}$ (Liter)	7,516	5,767	5,700	5,729	5,765

As well as, the optimum number of donations with AP and RP ways has been shown in table 6. 100% of the total produced PLSs are processed in BTC.

Table 6. The donations with AP and RP methods

Method	**Donation** (Times)	**Donation** (Liter)
AP	131,241	72,183
RP	455,844	82,052

The annual demand for each HCs and the PC under three different scenarios (optimistic, pessimistic, and realistic) are brought according to table 2 and table 3 according to the comment of the Iranian Blood Transfusion Organization. Table 7 shows a summary of the obtained results for the main variables without any scenario compared to without scenario.

Table 7. The results summary under three different scenarios compared to without scenario

Variables	Result			
	Pessimistic PS=25%	**Realistic** PS=55%	**Optimistic** PS=20%	**Without scenario**
Number of opened of CC	2			3
$\boldsymbol{VPP}$ (Liter)	65,013	71,029	77,040	95,636
$\boldsymbol{VSP}$ (Liter)	191,487	104,471	125,460	53,929
$\boldsymbol{Z}$, **The OF** ($)	70,734,540			51,118,152

4-2-Sensitivity analysis

Sensitivity analysis is the study of how the uncertainty in the output of a mathematical model can be divided and allocated to distinct sources of uncertainty in its inputs. The process of recalculating outcomes under alternative assumptions to specify the impact of a variable under sensitivity analysis will be useful for a range of purposes (Pannell, 1997; Saltelli, 2002; Saltelli *et al.*, 2008). Therefore, after solving the proposed mathematical model, we did sensitivity analysis on the model.

4-2-1-Demand

In this part, we discussed the effect of the variations of PLS for both therapy and medicine parts on the OF and the PLS shortage. For this situation, we assigned "0%" to a normal state then increased each time $\pm 20\%$ into the normal state. As depicted in figure 6, 20% enhancing of the medicine demand compare with the same increase of therapy demand, it can double the total cost and the shortage.

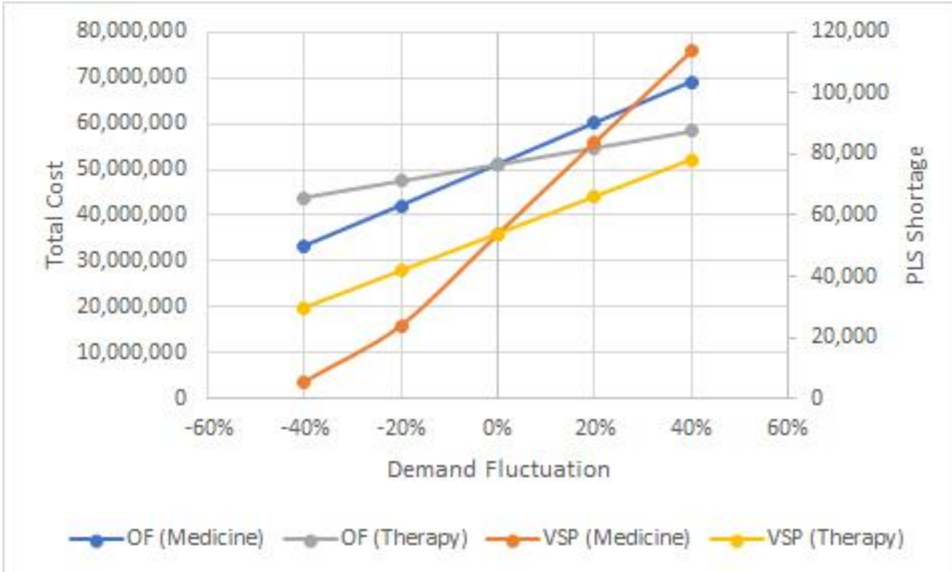

Fig 6. The effect of demand fluctuation on the total cost and the shortage

4-2-2-Capacity

In this section, we checked out efficacy the capacity of the AP and the RP on the OF and the PLS shortage. According to the results shown in figure 7, the $\pm 20\%$ fluctuation of the capacity of WB causes severe disruption on the OF and the PLS shortage.

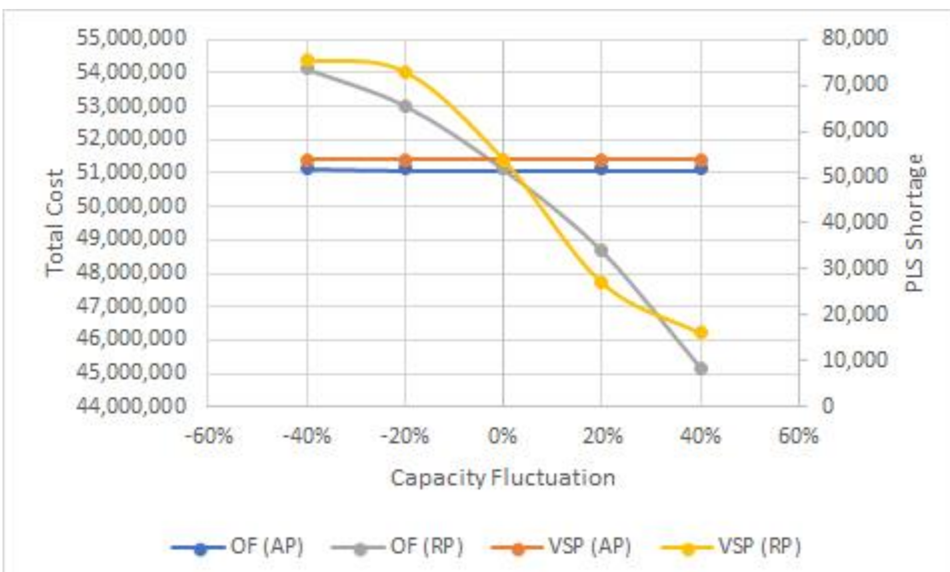

Fig 7. The effect of capacity of AP and RP fluctuation on the total cost and the shortage

4-2-3-Opening cost

In this segment, we investigated the result of the cost of opening of any CC on the OF and the PLS shortage. Illustrated in figure 8, the some fluctuation of the opening cost of every CC causes the severe disruption on the PLS shortage but its effects on the OF with a more gentle slope. Nevertheless, this steep slope is changing to a gentle slope (approximately fixed) after 200% for the PLS shortage.

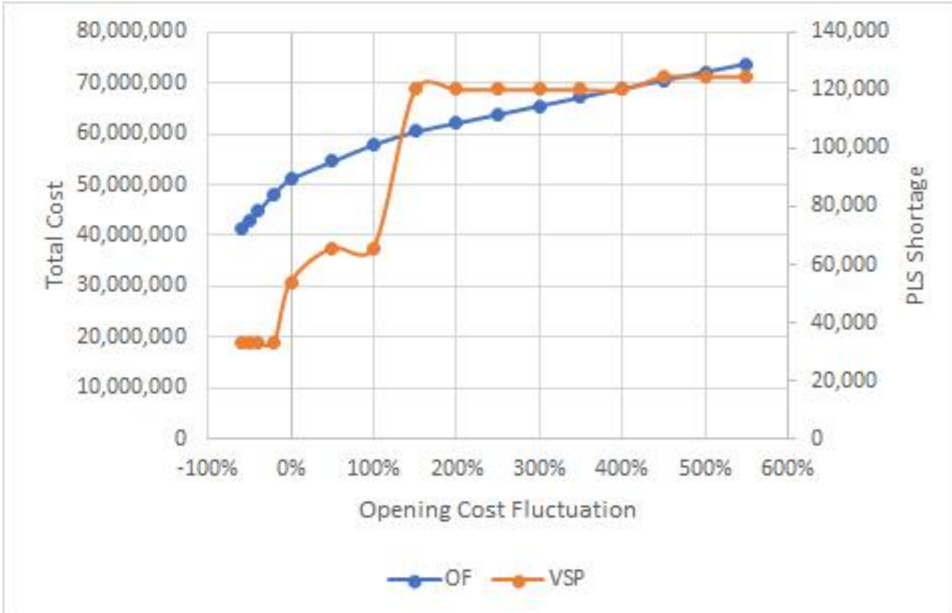

Fig 8. The effect of the opening cost on the total cost and the shortage

4-2-4-Transportation cost

At midnight on 15 November 2019, the Iranian government increased the price of petrol. Before the price increases, drivers could refuel to a maximum of 250 liters monthly (10,000 Iranian rial per liter). At the moment, drivers can refuel to a maximum of 60 liters monthly (15,000 Iranian rial per liter), then they can buy each liter with 30,000 Iranian rial. So, we are seeing an increase of 50% to 200% of the fuel price. In the following, we analyzed the effect of this increase on the OF and the PLS shortage. As demonstrated in figure 9, the variations of fuel cost (from free to 200%) have a few effects on the OF and it has zero for the PLS shortage.

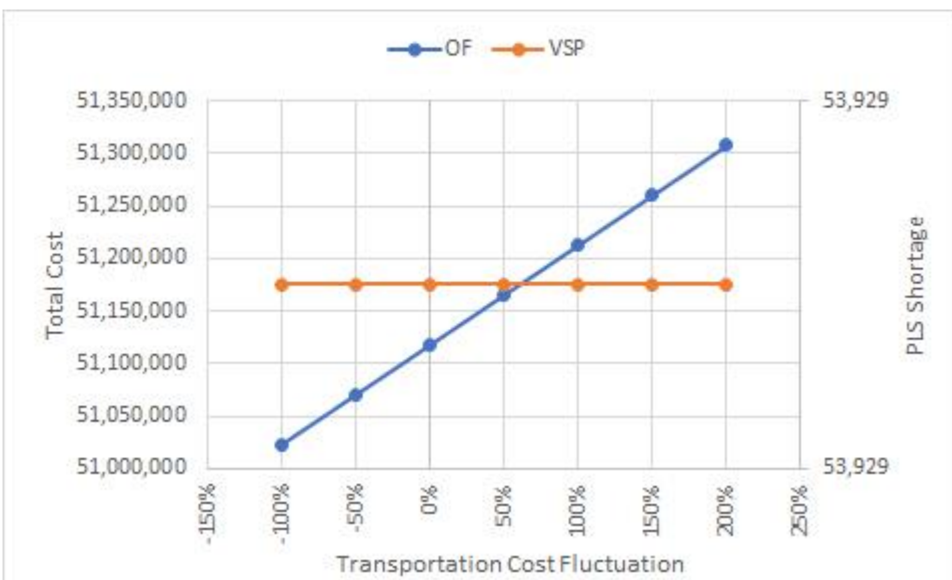

Fig 9. The effect of transportation cost on the total cost and the shortage

4-3-Managerial insights

In the end, some management strategies for efficient management of BPSC based on the obtained results of the proposed model were achieved. Through the analysis of the parameters and the variables (both positive and binary), we achieved the three significant results that are presented in the following:

- ❖ Due to segment 4.2.1, the sudden increase of PLS demand in the medicine segment disrupts the BPSC disrupts. Hence for the resiliency of the BPSC, we should be prepared enough. The best approach in this situation is adding the capacity of the RP, considering part 4.2.2.
- ❖ Due to section 4.2.2 and 4.2.3, the optimum method is the maximum use of the capacity instantly after the opening of each CC.
- ❖ Due to part 4.2.3, 50% raising the opening cost of each CC at two points (from 0% to 50% and from 100% to 150%) is very critical so the government must help the BTC in these two cases by subsidy to promote national health.

5-Conclusion and future research

Considering the blood plasma as a critical product in human life, this paper presents a MILP scenario-based mathematical programming model for designing an integrated blood plasma supply chain according to both therapy and medicine considerations for the first time. The previous research has not any attention to the medicine part; besides, the papers that paid about plasma in the therapy segment had less consideration to the special plasma features. In order to maximize the system's efficiency, the objective function considered tries to minimize total cost as well as unmet demand among demand points. Given the proposed model was novel, the actual data of a case study in Iran were used to illustrate the applicability also the performance of the offered model as well as validation. Obtained numerical results show the superiority of the recovered plasma method compared to the apheresis plasma method for the blood transmission network. As well, the maximum use of the capacity instantly after the opening of each collection centers is beneficial for reducing the total cost.

Further research is needed to extend the current work in several directions. The mathematical model developed in this paper could be extended by considering all blood products. Moreover, adding the multi-period planning horizon can be answering the short-life of some of the blood products such as platelet.

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