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Review

Plasma industry in Iran: Challenges and opportunities

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Abstract

Several studies have demonstrated the undeniable value of plasma as the source of myriads of proteins with numerous biological activities, many of which might not be discovered yet. Plasma fractionation is a process aiming at the production of plasma-derived medicinal products (PDMPs) such as gamma globulins (immunoglobulin [Ig]), hyperimmune serum globulins, albumin, and clotting and coagulation factors like Factor VIII (FVIII) and FIX. Despite several challenges in the evolution of the plasma industry, there is still worldwide increasing demand for PDMPs with the proof that the market size value of this industry is estimated at 28.69 billion dollars in 2021. In Iran, the plasma industry began its journey with the initial activities of the Iranian Blood Transfusion Organization (IBTO). Regarding the expense of establishing companies for plasma fractionation and elevating demands of PDMP in Iran's health system, decision-makers implemented contract fractionation which not only supply the needs of the country but also

cause significant savings in financial resources. Although the amount of collected plasma has been raised, more than 400,000 liters of collected plasma is still half of the required amount as Iran's demand for FVIII and albumin is over the supply. Putting together these data that the clinical indications for PDMPs, particularly IVIg, are growing (as seen in COVID-19) and commercially purchasing products is not economically beneficial, it is necessary for Iran's policymakers to invest in the plasma industry by establishing more plasmapheresis centers and raising people's awareness to donate more amount of plasma in order to elevate the levels of plasma collection annually. Moreover, entering the industry of fractionation by localization of this science and construction of fractionation plants should be on the agenda.

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1. Introduction

One of the principals of health care system is the availability of safe and efficient blood and blood-related products. Plasma and its related products are literally medicines manufactured industrially by pharmaceutical companies (1). The industry of plasma back in World War II when Dr. Cohn was commissioned by the U.S. to save the lives of soldiers (2). From then, development of the plasma industry resulted in the emerging of plasma-derived medicinal products (PDMPs) mainly consists of immunoglobulin (Ig), albumin, and coagulation factors (Factor VIII and Factor IX) which are life-saving agents and have been indicated in several chronic and acute life-threatening

disorders such as infections, immunological and hematological disorders, thrombotic diseases, and bleedings (3-5). Today, the conventional Cohn's method has been modified to generate the modern isolation of plasma products, so-called modern fractionation. Plasma fractionation plants run under strict conditions by observing hygiene and also infection removal strategies in compliance with good manufacturing practices (GMPs) (6).

The growing demands in the global markets have promoted the plasma industry towards high regulatory standards with more than 28 billion dollars in value (7) instead of medical service. The plasma industry is initiated from the collection systems and could be continued regarding the needs and infrastructures of a country whether in the domestic fractionation plants or in the contract fractionation performed by highly equipped fractionation companies (6). In Iran, the Iranian Blood Transfusion Organization (IBTO) was established in 1974 as a non-profit organization with the objective to manage all activities regarding blood transfusion from donation to distribution. IBTO came into the plasma industry but immediately faced challenges such as transfusion-transmissible infections (TTIs) or high prices of the establishment of domestic fractionation centers. In order to shed light on the plasma industry in Iran, this review aims to cover a glance at the history of plasma fractionation and discuss this industry by illuminating the supply and demand as well as the challenges and opportunities facing the plasma industry in Iran.

2. A glance at the history of the plasma industry

Early attempts regarding the industry of plasma back into the career of Dr. Edwin Joseph Cohn, a protein scientist and an expert in the physical chemistry of proteins, who was commissioned by the U.S. Navy in World War II with the aim to purify a stable blood substitute for injured soldiers (2). Cohn's efforts led to the purification of stable albumin an acceptable clinical effectiveness to compensate for the blood loss in acute hemorrhage (8). The investigation of Cohn and his team continued after the war with the purpose of attaining plasma products from the nascent fractionation industry with the highest quality (9). For the first three decades, it was albumin that was maintained as the industry's staple; however, by the late 1940s, other noteworthy fractions were identified by Cohn's team, many of which have clinical indications nowadays (10). Accordingly, application of human antihemophilic factor (Factor VIII) as one of the initial therapeutic methods for hemophilia A (11) or utilizing Ig for the treatment of Bruton agammaglobulinemia (X linked agammaglobulinemia [XLA]) (12) are examples of PDMPs in addition to albumin which were prepared based on Cohn's method.

These reports shed light on some concepts declaring the availability to harvest several factors from one donation, or even the plasma donations could be pooled. In the late 1950s, Cohn's team investigated the early FVIII fraction from the plasma which unfortunately was hardly stable and poorly soluble, thus wasn't proper for hemophilia therapy (13). In the following, the application of the cryoprecipitate fraction of plasma to reach a concentrated form of FVIII by Pool's efforts revolutionized the context of PDMPs (14). A few years later, the technology of cold insoluble fraction of plasma to higher the concentration of extracted stable FVIII was adopted in the industry (15). It should be stated that it was those efforts from the late 1960s to the late 1970s that alter the shape of hemophilia from an enfeebling disease to a manageable disease with close-to-normal lifestyle conditions (16). In the early 1970s, to manage the life-threatening manifestation of growing numbers of hemophilia patients, higher amounts of FVIII fraction were required which made FVIII the pioneer of PDMPs instead of albumin (13).

In the 1980s-90s, two significant events were about to shut down the whole plasma industry. One was the tragic viral epidemics in individuals with hemophilia (17) which was managed by development of safe manufacturing techniques. The other was the progression of recombinant products in the late 1980s which was predicted to be able to limit the plasma industry (18); in fact, those events didn't shrink the plasma industry but the victim was FVIII which lost its pioneer role in this industry. Thus, in the early 2000s, it was the turn of another plasma molecule to bear the burden of the growing plasma industry, Ig. The indications for the application of intravenous polyvalent Ig rapidly provide a lead position for this protein in this industry. With this regard, attaining a protocol to modify Cohn's method in order to change the route of PDMP administration to an intravenous route extremely elevated the need for intravenous Ig (IVIg) for patients with primary immune deficiency (PID) (19). Similarly, the application of IVIg in some cases with neuropathy as immunomodulatory factors (20) raised its demand, for the benefit of the plasma industry.

Nowadays, the initial Cohn's method is still utilized typically for the extraction of albumin products; this

method was based on forming a solubility difference (usually by ethanol) between the intended protein (higher solubility) and other proteins (lower solubility) resulting in the deposition of other proteins or vice versa (8). The demands for Ig fraction are at the highest levels which necessitate continuous technological alterations in order to enhance the quality of yielded Ig product as well as its safety (13). For example, novel chemistries have been developed to extract Ig from the plasma of HCV+ chimpanzees without any risk for virus transmission by an infection-neutralizing method (21). Also, the fractioning of less economically important products like Antithrombin III and FIX have been performed by methods different from Cohn's such as chromatographic techniques (22, 23).

Apart above-mentioned aspect of the plasma industry, it is worth noting to have a glance at how plasma collection method has grown. Prior to the 1980s, conventional plasma was obtained via the centrifugation of whole blood yielding a separated plasma bag (called recovered plasma). However, it was in the 1980s that the development of automatic plasmapheresis machines provided a novel, safer and more efficient method to separate plasma (called source plasma) (24). In the U.S., 5.4 million liters of source plasma were collected in 1978 which reached 12 million liters in 1996 and was diminished to 9.6 million liters in 2000 regarding the restriction of strict enforcement of GMP by FDA (25). Currently, about 65% of collected plasma was obtained by the apheresis method and the rest as recovered plasma (6). To provide a better overview, a history of the plasma industry is provided in **Figure. 1**.

3. A glance at the clinical importance and indications of plasma-derived medicinal products

Generally, the collection of plasma can have two destinations either as a therapeutic product (called clinical plasma or fresh frozen plasma) which could be utilized in the treatment of some blood-related disorders such as immune thrombocytopenic purpura (26) or as a source for pharmaceutical fractionated products (called plasma products or plasma derivatives) which have clinical indications in a variety of diseases. Several studies have demonstrated the noteworthy of plasma as the source of myriads of proteins with numerous biological activities, many of which might not be discovered yet. Indeed, out of 60 g protein in each plasma liter, 55 g could have potential clinical indications (27). These features facilitate the PDMP to be utilized as therapeutic agents in several disorders including life-threatening diseases such as hemophilia, immunological disorders, diseases related to tissue degeneration, infections and related pathologies, injuries associated bleeding, and thrombotic disorders implying the great capacity of the plasma industry in clinical applications (6, 28). Most of the plasma proteins consist of albumin at 35 g/L and IgG at 10 g/L which together form almost 80% of all proteins of the plasma. There are also low-in-frequency but potent active proteins such as α1-antitrypsin (AAT) (1.5 g/L), antithrombin (AT) (300 mg/L), and also FVIII (100-200 ng/L).

3.1. Albumin

Being the most abundant plasma protein, albumin is synthesized in the liver and is responsible for 80% of the colloid osmotic pressure of plasma (29). Regarding crucial biological and biopharmaceutical functions of this protein, the need to replenish its loss after pathological situations such as surgery is elevated (29, 30). Besides regulating plasma oncotic pressure, albumin can bind to several blood proteins such as drugs and act as a drug carrier (31, 32), or gases and metabolites. Albumin can also serve as a chaperone by modulating the folding of numerous proteins and limit their pathologic accumulation (33). By deactivating different kinds of oxidative agents such as reactive oxygen species and reactive nitrogen species, albumin plays as an anti-oxidant agent regulating the oxidative condition of blood, as well (34, 35). Hypovolemic conditions __as seen in situation like emergency treatment of shock, acute burn, and restoration of blood volume__ are out of the main indications of albumin product. Apart from these roles, we have to mention that the levels of albumin could be dysregulated in several pathological conditions including liver disorders, inflammatory diseases like rheumatoid arthritis, cancers like brain tumors, kidney disease, cardiovascular risk disease, and blood sugar dysregulation (36-40); further highlighting the need for a higher amount of plasma-derived albumin in the future. The albumin product is prepared in two forms based on the requirement; one is albumin 4-5% (almost similar to iso-oncotic solution) and the other is albumin 20-25% (higher than iso-oncotic solution) (41). Situations like emergency hypovolemic shock, acute liver failure, and cardiopulmonary bypass need immediate action using albumin 4-5% (42, 43). However, albumin 20-25% could be clinically utilized in conditions such as hypoproteinemia, acute respiratory distress syndrome (ARDS), acute

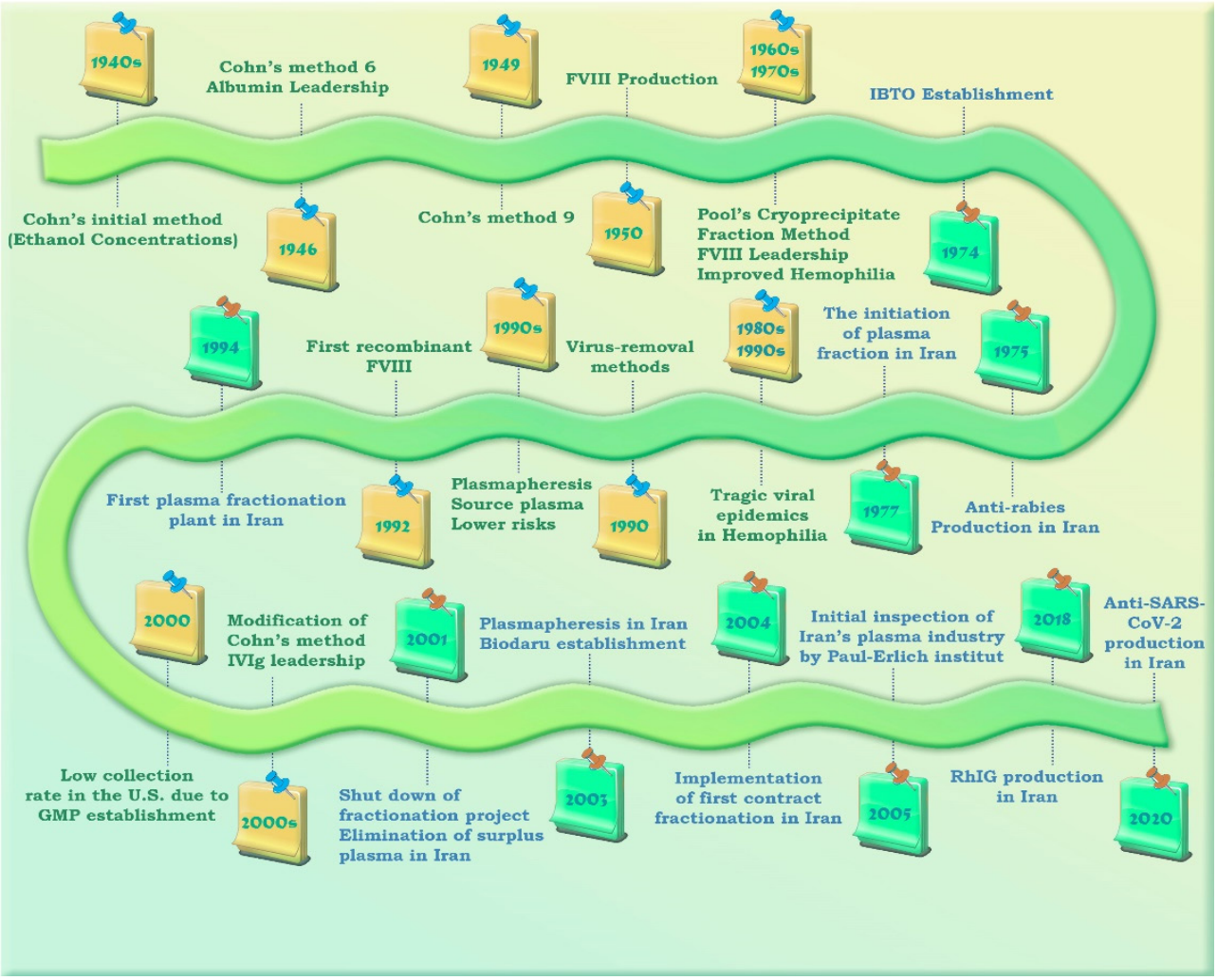

Figure 1. **The history of plasma industry in a timeline.** First concepts regarding the fractionation of plasma back in the 1940s when Dr. Cohen was commissioned in World War II to save the lives of injured soldiers by means of blood-related products. The initial plasma fractionation method invented by Cohn was changed in 1946 (Cohn's method 6) and 1949 (Cohn's method 9); however, the main plasma-related product was the albumin utilized in the war and after that. In 1950 the attempts of Cohn's team led to the separation of FVIII from plasma, a miracle for hemophilic patients, but it was unstable and had low solubility. Thus, the innovation of Pool in utilizing the cryoprecipitate fraction of plasma led to the attainment of appropriate FVIII concentrate in the 1960s. The vast application of FVIII in improving the quality of life of hemophilic patients caused the replacement of albumin with FVIII as the new leader of the plasma industry. It was in 1974 that IBTO was established and from the very beginning started the production of anti-rabies production. In 1977 Iran owned a primary fractionation system; however, the tragic viral epidemic in the 1980s and 1990s led the plasma industry to the brink of shutting down worldwide. Despite the development of virus-removal methods in 1990, Iran's progression in this context was limited. The gap in the plasma industry due to the viral epidemic resulted in the advancement in recombinant techniques and led to the first recombinant FVIII production in 1992. In the plasma industry, the development of plasmapheresis in the 1990s improved the plasma collection systems, and source plasma emerged. In Iran, the first plasma fractionation plant was established in 1994; however, due to economic burdens and limited progression in the virus-removal methods, the project of domestic plasma fractionation in Iran was shut down and the surplus plasma was eliminated in 2001. It could be stated that the 5.4 and 12 million liters of extracted plasma (source) in the U.S. in 1987 and 1996, respectively experienced a reduction and reached 9.6 million liters in 2000 because of the pressure of competent regulatory authorities and inappropriate establishment of GMP system. Nevertheless, the expansion of IVIg indications as a potential regulator of dysregulated responses made this PDMP the new leader in the plasma industry in the 2000s. In 2003, the first plasma collection center was established in Iran (Biodarou) to increase the amount of plasma collection for contract fractionation which was initially implemented one year later, in 2004. The inspection procedure of Iran's plasma was started in 2005 by Paul-Ehrlich Institut and similar organizations. Since then, several contract fractionations have been implemented to supplement the PDMP of Iran. Nonetheless, the low-scale attempts of Iran to fractionate its own plasma with its own facilities led to the production of RhIG in 2018 and anti-SARS-CoV-2 in 2020.

nephrosis and liver failure, hemolytic disease of the newborn (HDN), and treatment of burns (29).

3.2. Coagulation factors VIII and IX

FVIII is probably best known for its roles in hemophilia. Hemophilia A and B are rare diseases caused by the presence of deficiency or dysfunction of FVIII and FIX, respectively due to genes mutations in chromosome X. Obviously, lack of appropriate coagulation factors in hemophilia patients could result in bleeding symptoms mainly in muscles and joints leading to musculoskeletal chronic injuries. Besides, hemophilia patients are extremely vulnerable to trauma and surgical interventions due to the risk of severe uncontrolled bleeding (44). The lack of FVIII could be observed, in a weaker form, in von-Willebrand disease (vWD). Although vWD is not a coagulation disorder, a deficiency of FVIII secondary to the primary defect is usually reported. In type 3 vWD cases who have moderately severe FVIII deficiency, hemarthrosis and postoperative hemorrhages, and generally bleeding in soft tissues is common (45).

The notable industrial development of freeze-dried plasma concentrates of FVIII in the 1970s revolutionized the treatment of patients with hemophilia A as well as hemophilia B due to the presence of other coagulation agents in the collected plasma such as Factors II, VII, IX, and X. These plasma products had advantages such as simple storage in refrigerators and availability in small amounts (44). Nonetheless, the tragic event in the 1980s (the transmission of fatal blood-borne viral infections like HIV and hepatitis) remarkably slowed down the whole plasma industry. However, the development of virucidal and virus-removal methods and adding them to the plasma industry made plasma-derived coagulation factors sterile and safe to use so that no plasma-related viral infections were reported in the late 1980s and early 1990s. The gap in the plasma industry due to virus transmission risks together with noteworthy progression of molecular medicine in that times resulted in the development of recombinant Factors VIII and IX as therapeutic agents in the 1990s (17).

Years after recombinant factors development, unsolved questions were emerged indicating the high risk of generation of inhibitors (antibodies) against FVIII in previously untreated patients (PUPs) who treated with recombinant FVIII. To address this issue, two systematic reviews from retrospective and prospective studies evaluated the presence of inhibitors in patients receiving recombinant FVIII compared with plasma-derived FVIII which showed higher incidence of inhibitors in recombinant FVIII (27.4% vs 14.3%) (46, 47). The first randomized-controlled clinical trial (SIPPET) also demonstrated remarkably higher development of inhibitor antibodies in patients receiving recombinant FVIII in comparison with plasma-derived FVIII (44.5% vs 26.8%) (48). Due to the equal effectiveness of plasma-derived FVIII and recombinant FVIII in hampering the bleeding, the incidence of inhibitors should be the first priority in choosing therapy (49).

3.3. Immunoglobulin (Ig)

The initial attempts for the application of Ig back in the 1950s and 1960s when the administration of intramuscular Ig was considered the first-line treatment for patients with inherited IgG deficiency (50-52). Regarding the presence of impurities and Ig aggregates and the risk of complement activation and anaphylaxis, the administration of IVIg was not possible (53). In the 1979, manufacturing of Ig extraction was modified and initial safe IVIg was administered with low toxicities. Nowadays, Ig is the chief product of the plasma industry, and extracted from large pools of human plasma generating proper concentration of IgG as well as IgA (54) and IgM (55). By using the ultrafiltration method, the final product of Ig is concentrated and formulated for clinical use (56). The Ig product extracted from plasma contains several specific immunomodulatory antibodies allocating the IVIg therapeutic method the capacity to improve all aspects of the immune system (57). Accordingly, Increasing evidenced has shown that IVIg has a potent indication in the treatment of inflammatory diseases and autoimmunity (58). In this context, 2g/kg body weight of IVIg is required in order to double the concentration of IgG in the blood (59, 60). The potential of IVIg in the treatment of autoimmune disorders is obtained even at lower concentration by exhibiting boosted pharmacological efficacy (61). It was shown that pre-inflammatory conditions mediated by neutrophils, eosinophils, and cytokines could enhance the sensitivity of the immune system to IVIg therapy (62, 63). IVIg could be a beneficial treatment in conditions like Guillain-Barré syndrome, systemic lupus erythematosus (SLE), ANCA-associated vasculitides,

and idiopathic inflammatory myopathies (64).

Besides, IVIg has also a vast range of indications from primary and secondary Ig deficiency syndromes to infection-related disorders. This product is the first-line treatment of several disorders like idiopathic thrombocytopenic purpura (ITP), thrombocytopenia (neonatal alloimmune, fetal, and HIV-associated), post-transfusion purpura, acquired hemophilia, acquired vWD, and also autoimmunity (55). Plasma-derived Ig interacts with several pathogens thus IVIg could target an array of bacteria such as Streptococcus pneumoniae, Mycoplasma pneumoniae, Helicobacter pylori, and Klebsiella as well as viruses like measles, mumps, rubella, Epstein–Barr virus, and herpes virus (65). Due to the capacity of IVIg in regulating several immune compartments such as neutralizing autoantibodies, complement system, antigen presentation, and T helper functions, this therapeutic approach found a novel indication in the recent coronavirus pandemic, COVID-19. According to 4 clinical trials and 3 cohort studies, administration of IVIg in COVID-19 patients results in a reduction in mortality rates and shows clinical efficacy (66).

3.3.1. Hyperimmune plasma in Iran

Since the 1970s, the IBTO produced anti-rabies specific Ig as one of the first plasma products in Iran. The evaluation of anti-rabies titer in volunteers who had a history of the infection or vaccination could indicate the appropriate donor for anti-rabies. The generated anti-rabies product was delivered to the Pasteur Institute of Iran as the treatment agent. Following the shutting down of plasma fractionation plants in Iran, the production of the anti-rabies product was assigned to the Biotest (Germany) which is a fractionator and now this contraction is yielding several amounts of anti-rabies product. However, due to economic difficulties and a shortage of anti-rabies products in Iran, the production of this PDMP was continued in IBTO parallel with the contract fractionation. Nevertheless, the demands for this product in Iran are still surplus the supply implying the need for providing higher amounts of anti-rabies product.

Rho(D) immune globulin (RhIG) is one of the important kinds of Ig which has indication in RhD-mothers in order to inhibit RhD isoimmunization. Since 2018, the project of producing RhIG was initiated in Iran, however, it is a complicated process faces several limitations regarding the recruitment of appropriate donators. In late 2018 and early 2019, the experimental stages of the production of RhIG and approval were carried out, but currently, the production of an industrial sample of this product is still in doubt.

As stated, one of the recent applications of IVIg was in patients with COVID-19. As no promising therapeutic approaches were presented, and regarding the experience of IVIg therapy in similar viral infections like SARS, the application of IVIg was considered as one of the available therapies. In Iran, the application of IVIg in COVID-19 patients was initiated at the beginning of the COVID-19 pandemic. The collection of plasma was carried out in mobile units as well as plasma collection centers. In the following, the process of plasma collection for COVID-19 patients was centralized in IBTO. Although the efficacy of IVIg in COVID-19 showed controversial data, data from Iran showed that the IVIg therapy was effective only in the first week from the onset of the disease. By the end of 2021, 18,000 units of plasma were collected and 15,000 of them were utilized in COVID-19 cases. Nevertheless, due to controversial data and vaccination, the application of IVIg in COVID-19 and consequently the collection of plasma with this purpose got limited. **Table 1** provides details about PDMPs and their clinical indications.

4. Plasma industry in Iran

Back in 1974, the government of Iran established IBTO in order to centralize the transfusion system. IBTO has been a public and non-profit organization but under control of national health authorities (67, 68). Since 1974, the blood component demand of Iran has been met majorly via voluntary and in a small amount by family replacement donors instead of paid blood (69). It could be stated that the official plasma industry in Iran was established in 1977 when own fractionation facility of Iran produced PDMPs. Regarding the absence of valid virucidal and virus-removal methods in the 1990s, the production of PDMPs, particularly coagulation factors, was terminated. Since then, significant Iran's demand for plasma products has been provided by importing PDMPs. In today's health programs that several countries have developed infrastructures for the plasma industry to improve the efficacy of PDMPs, Iran had also plans for establishing a fractionation facility, but technical

Table. 1 **The stage of PDMP fractionation and their clinical indications.**

Product	Proportion of plasma	Stage of fractionation	Clinical indications
Albumin	65%	Fraction V, from Effluent IV-1	Regulation of plasma oncotic pressure, Hypovolemia conditions, Acute burns, Emergency shocks, Acute nephrosis and liver failure, Cardiopulmonary bypass, ARDS, and HDN
IVIg	30%	Fraction II+III, from Effluent I	ITP, Neonatal alloimmune, fetal, and HIV-associated thrombocytopenia, Post-transfusion purpura, Infections such as SARS-CoV-2, Inflammatory and autoimmune disorders such as Guillain-Barré syndrome, SLE, AAV, and myopathies
FVIII	5%	Cryoprecipitate, from Pool plasma	Hemophilia A and vWD
FIX		Effluent I, from Cryo-poor plasma	Hemophilia B
Fibrinogen		Fraction I, from Cryo-poor plasma	Afibrinogenemia, Hypofibrinogenemia, Dysfibrinogenemia, Massive and childbirth hemorrhage, DIC, Liver disorders, and Cardiac surgery
vWF		Cryoprecipitate, from Pool plasma	Von Willebrand disease

ARDS: Acute respiratory distress syndrome; **HDN:** Hemolytic disease of the newborn; **IVIg:** Intravenous immune globulin; **ITP:** idiopathic thrombocytopenic purpura; **SLE:** Systemic lupus erythematosus; **AAV:** ANCA-associated vasculitides; **FVIII:** Factor VIII; **vWD:** Von Willebrand disease; **FIX:** Factor IX; **DIC:** Disseminated intravascular coagulation; **vWF:** Von Willebrand factor.

difficulties as well as economic issues hampered its development (68). On the other hand, the worldwide market for pharmaceutical plasma products experienced a deficiency regarding PDMP possibly due to the limitation of raw materials and remarkably higher world demands. Consequently, the supply-demand balance in the market of plasma industry felt instabilities, and as a result, the global price of PDMPs was raised.

4.1. Contract fractionation

According to the Iran's law, IBTO is the only source of blood donation; thus, even if there could be enough fractionation facilities (which are not), all needs of PDMPs could not be covered. Also, the costs of importing those medicines to cover the rest of demands are notably high. Also, a high amount of collected plasma in 2001 were dedicated to fractionation programs; however, because of the closure of fractionation plants in Iran and due to high costs of maintaining plasma, those plasmas were eliminated. Hence and for the mentioned reasons, Iran Blood Research and Fractionation Co. (IBRF), a sister company of IBTO, implemented a contract fractionation project with corresponding companies abroad instead of establishing a domestic plasma fractionation facility. Initially in 2004, two commercial companies in France and Germany were the destination of plasma generated by IBTO in contraction based on 15,000 liters at first, and 70,000 liters and 65,000 liters in the following (68). From 2004 to 2007, the blood collection in IBTO was evaluated by the auditors of European regulatory authorities and the Paul-Ehrlich Institut for inspecting the cold chain system to ensure the safety of quality of exported plasma. The auditors didn't mention any significant error expect in the context of documentation implying the quality of blood collection system carried out by IBTO. The contract fractionation also made IBTO to improve the criteria of blood transfusion safety to reduce the risk of TTI which actually yielded beneficial outcomes. Besides, according to the contraction, the fractionators should assess the possibility of TTI by evaluating the presence of HBV, HIV, HCV, HAV, and parvovirus B19 using nucleic acid testing systems (69). Nonetheless, implementation of a contract fractionation could face some challenges such as the selection of fractionators (companies), the duration of contract, plasma volume shipment, the inspection of audits, the transportation of plasma across international borders, maintaining cold chain system, and performing nucleic acid tests for TTI (70). As part of medicinal products, the PDMPs whether obtained from recovered plasma or imported sources must be officially approved for their marketing authorization by the National Regulatory Authority (NRA) in the Ministry of Health. Indeed, this supervision could enhance the quality and safety of extracted plasma which are required for PDMP production. The NRA of Iran inspects contractor site and is continuously assessing all batch release documents before issuing marketing authorization for PDMPs. All in all, the outcomes of the 2004 contract fractionation were

supplying 44% of IVIg and 14% of albumin market demands, and unfortunately, the amount of FVIII was not sufficient to meet the demand of market in Iran (69).

IBTO also made a contraction with Octapharma (Switzerland), Biotest (Germany), and CSL Behring (Australia) in order to produce albumin, IVIg, FVIII, and FIX from recovered plasma. Indeed, the strategy of implementing contraction with various companies was because of the possibility of economic and political difficulties which could limit the process of exportation of plasma and importation of PDMPs. In 2006, 50,000 liters of plasma under supervision of IBTO were imported to the Biotest (Germany); of note, this company was the destination of a major proportion of Iran's exported plasma from 2005 until 2015 which reached the highest level in 2011 (about 140,000 liters) (70). From 2016 to 2019 the amount of collected recovered plasma was reduced remarkably due to diminished trend in blood donation rate from 27/1000 persons to 25/1000 persons.

As stated, the contraction with fractionators is the main method by which the country provides the requirement of PDMPs. To improve the cost effectiveness of plasma industry, each amount of plasma must be utilized as many PDMP as possible. With this regard, one liter of Iranian recovered plasma yielded 4.5 g Ig, 24.5 g albumin, 160 IU FVIII, and 200 IU FIX according to contract fractionation program. In 2011, the yielding outcome was improved and almost all the demands of Iran for IVIg as well as FIX were supplied following the contract fractionation program; however, 40% of albumin need and only 15% of FVIII need were provided (71) (**Figure. 2**); concerning why FVIII was low, investigations showed that some Iranian FVIII is wasted during the separation, storage, and transportation of plasma (72).

4.2. Plasma collection system; the emergence of source plasma

Regarding high global demands for PDMPs in pharmaceutical market, the only recovered plasma could not meet the demands, and thus, the source plasma was emerged. The mission of IBTO is essentially directed to improving the national transfusion system meaning that the market of PDMP is on the second stage. Therefore, IBTO has have no intention to elevate unnecessary blood collection to produce plasma products; however, a project to stablish plasma collection system inside the IBTO caters was started in 2015, but it was shut down in 2019 due to some conflicts in policies. Nevertheless, plasmapheresis centers outside of IBTO were established with the mission to increase the volume of produced plasma.

Darman ara company (Iran) is one of the first companies in plasma collection. Indeed, they were Biotest representative and the idea of establishing plasma collection centers came from this company. Accordingly, Biodarou (Iran) which is the subsidiary of Darman ara and a center for plasma collection and importation of PDMP was established in 2003. The association of Biodarou (Iran) and IBRF resulted in the establishment of more plasmapheresis centers in association with Biotest (Germany) and Octapharma (Switzerland) in order to increase the capacity of plasma collection. The deputy manager of Biodarou declared that until 2020 Iran collected 350,000 liters plasma per year (73, 74), which reached higher than 400,000 liters annually in 2022 (75).

According to a recent study that evaluated 16 centers of plasmapheresis in 11 cities of Iran between 2016 to 2019, 85,515 first-time and 8,559 repeated donors were recruited over four years. While 230,000 donations were lost from 2016 to 2019 which resulted in 46,000 liters reduction of plasma, those plasmapheresis centers collected 49,203 liters plasma. Also, the positive rate of HCV was 0.019% which all of them were from first-time donors (76).

5. Plasma economics

Plasma is a raw material that consists of several important ingredients. Economically, the price of 1 liter of high-quality plasma which passed the quality controls and investigation assessments is equal to 45% of overall finished product's cost, making plasma one of the most important factors in the cost of end-products when comparing with other pharmaceutical industries with the percentage of 5% (77). It could be inferred that the total plasma fractionation volume and plant throughput is strongly associated with the demand for the related therapeutic medicines (78). In 2009, total market for PDMPs was 11.8 billion dollars (25); between 2016-2018, the worldwide demand for PDMPs direct the related market to yield 21,174 billion dollars (79). Accordingly, IVIg had the greatest proportion of PDMP marketing with 47.3% (about 12 billion dollars) of total market and albumin (15.7%), FVIII (7.6%), and FIX (1.5%) were in the next ranks (the rest were other proteins derived from plasma) (80) (**Figure. 3**). As is clear, IVIg is the driver of the

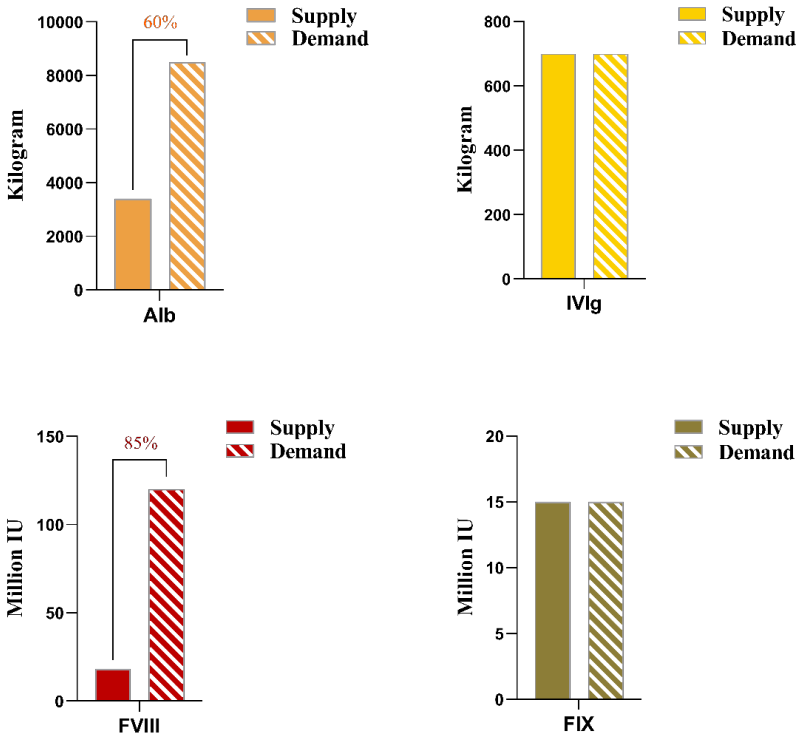

Figure 2. The estimated supply and demand of PDMP in Iran in 2011 (71). The implementation of contract fractionation in Iran yielded 3400 kg albumin, 18 million IU FVIII, 15 million IU FIX, and 700 kg IVIg in 2011. Although this contraction provided IVIg and FIX surplus the demands of Iran (17.6% and 25% higher amounts), albumin and FVIII are still 60% and 85% below the demand levels of the country, respectively. Thus, more increased amount of plasma is required to make a high-load contraction for higher-yielding albumin and FVIII due to the inevitable roles of these agents in enhancing the health levels of patients, particularly hemophilic ones.

plasma industry so that required plasma volume is tightly associated with the global demand for IVIg (81).

A recent analysis showed that the global plasma fractionation market size was elevated to 28.69 billion dollars in 2021. It is estimated that the value of this market raises to 49.61 billion dollars by 2029, demonstrating a compound annual growth rate (CAGR) of 7.1% within the predicted period. According to 2021 data, IVIg still takes the lead in plasma industry acquiring more than 50% of the market. Albumin and FVIII have equal shares in the second rank and protease inhibitors and other proteins follow them (7). In 2021, the application of PDMP was higher in the context of neurology due to the elevated demands for IVIg in pathological conditions such as chronic inflammatory demyelination polyneuropathy, multifocal motor neuropathy, myasthenia gravis, and so on (82). Of note, the largest regional market for the plasma industry was North America in 2021 with 16.1 billion dollars in value (7).

5.1. Plasma economics in Iran

Although the collected plasma (recovered) was from voluntary non-remunerated blood donation (VNRBD) meaning that no profit could be obtained, the preservation of the plasma and providing situations for contract fractionation had costs. With this regard, in 2005, IBTO was allowed to consider 500,000 rials for each liter of plasma and add it to the final price of PDMPs in order to compensate the mentioned costs. According to the fact that blood-related components are available free of charge in Iran and also PDMPs are distributed between patients as medicines; thus, they require to be paid. Some of them like FVIII and FIX are subsidized by the government and the others such as Ig and albumin should be paid whether by patients themselves or insurance companies. Nevertheless, the operational costs of IBTO and IBRF as non-profit organizations such as plasma extraction and preparation, the transportation, and fractionation (contract fractionation costs, overhead and administration costs, and costs related to running and expanding the program) should be supplied by

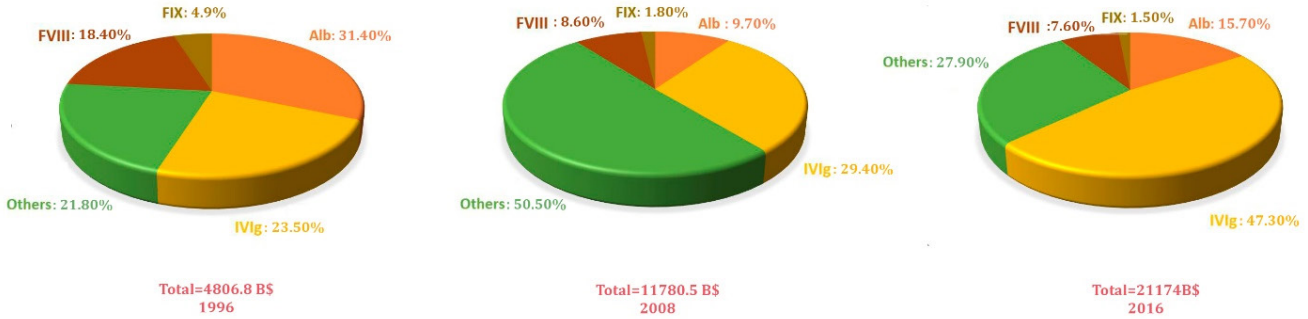

Figure 3. **The total market of plasma in billion dollars and the proportion of each PDMP in 1996, 2008, and 2016.** Obviously, the total market of the plasma industry grows over the years. Alongside the elevated value of the market, the so-called leader of this industry has been changed due to the global demands for PDMPs. Initially, the major component of plasma was albumin which has various indications in clinical situations such as injuries, surgeries, and liver dysfunctions. However, more understanding of Ig roles in modulating pathological conditions such as hyperinflammatory responses altered the leadership of the plasma industry towards Ig which has been recently used as IVIg. The proportion of coagulation factors (FVIII and FIX) was initially higher but gradually decreased due to the emergence of recombinant techniques. Nevertheless, regarding the induction of inhibitors (antibodies) and higher prices of recombinant FVIII and FIX, the plasma-derived FVIII and FIX are still deserving therapeutic medicines in coagulation disorders like hemophilia. Taken together, concerning the particular features of IVIg, it seems that the clinical applications of this PDMP are going to grow and much more attention should be directed to the plasma industry (source: Marketing Research Bureau, Inc.).

provided products. According to 2010 data, the average price of IVIg for contract fractionation program was 29.5 €/g while in the market it was 40 €/g. Similarly, the average price of albumin, FVII, and FIX was 1.9, 0.20, and 0.21 €/IU, respectively which was lower than the average market (2.3, 0.22, and 0.25 €/IU)(**Figure. 4**).

These data strongly suggest that commercially providing those medicines is more expensive than PDMP provided by contract fractionation. All in all, the operation of contract fractionation by Iran Ministry of Health saved 8.5 million euros for the national health care system (71). **Figure. 5** summarizes the profits of the plasma industry in Iran. By comparing the demand of PDMP in Iran and the amount of yielded PDMP in the contraction manner, Iran is still lower than market demands. **Table 2** provides information about the supply and demand of PDMP and relative prices.

6. Challenges and opportunities

The risks of TTI (particularly viruses) and the costs of virus-removal methods are always a challenging issue that could not be overlooked, specially following the tragic occurrence in the 1980s about HIV and HCV infections (83). After 1984, the neglected virucidal and infection-removal methods were added to the process of plasma production (84), which in turn raised the ultimate cost of plasma product (85, 86). On the other hand, as the transmission of viruses is tightly associated with the incidence rate of infections in the donors, the monitoring of any possible infection before the donation process seems logically acceptable (87). Nonetheless, it could be concluded that performing a risk assessment evaluating the whole plasma product industry could shed light on how much the virucidal methods show benefits when we considering the risks of HCV and HIV as TTI (1 in 1 million blood bags) or HBV (1 in 500,000 blood bags).

The establishment of plasma fractionation plants is certainly the ultimate target in the plasma industry, and currently, the market of plasma industry is in the authorities of large companies around the world. **Figure. 6** provides the numbers of plasma fractionation plants as well as the chief proportion of global plasma fractionation by regions. Indeed, if a country has a fractionation plant, it is necessary to be supplied by sufficient amount of plasma in order to produce as much as possible plasma-related products; this means that all collected plasma should be directed to the fractionators if they have enough capacity. Moreover, by enhancing their capacity, plants could make requests to recruit plasma from abroad, meaning that they are eligible for importation of plasma and exportation of PDMPs that consequently make fractionators valuable units in the economy of the country (78). **Figure. 7** demonstrates the amount of collected plasma globally. In Iran, the demands of the market could not be

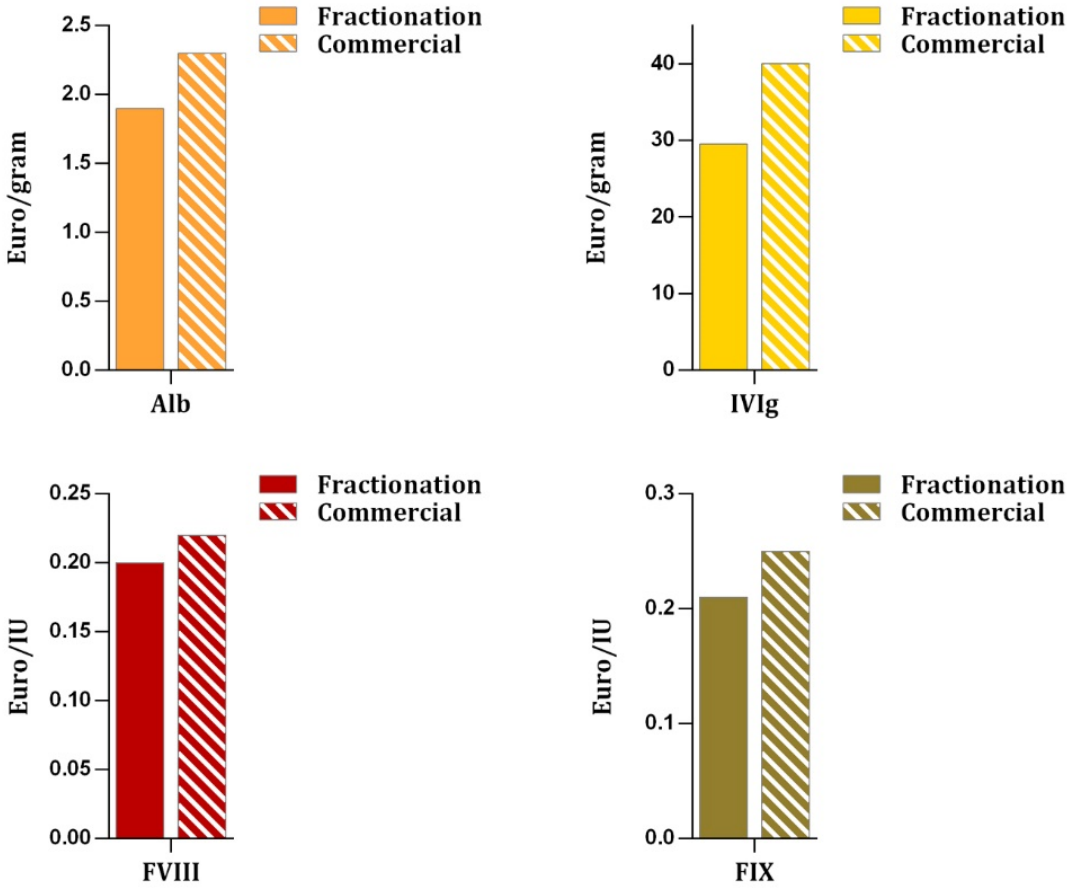

Figure 4. **The difference between fractionation-provided PDMP and commercially-purchased products.** Comparing the prices showed that in each component, i.e., albumin (1.9 €/g vs 2.3 €/g), FVIII (0.2 €/IU vs 0.22 €/IU), FIX (0.21 €/IU vs 0.25 €/IU), and IVIg (29.5 €/g vs 40 €/g) the price of PDMP yielded in the contract fractionation is lower than their relative commercial prices implying the economic advantages of PDMP in the contract fractionation.

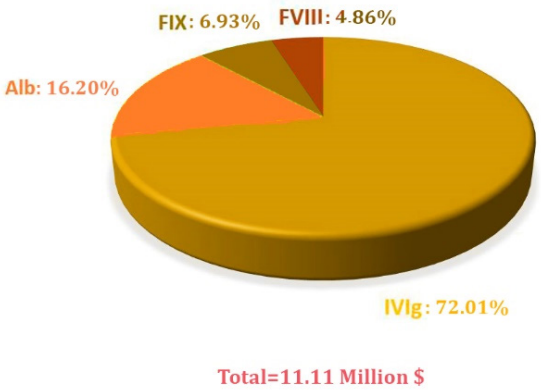

Figure 5. **The profits of the plasma industry in Iran.** The illustration shows that the plasma industry in Iran saved 11.1 million dollars in 2011 by implementing contract fractionation. The proportion of IVIg is more than 72% (8 million dollars) that is followed by albumin with 16.2% (1.8 million dollars), FIX with 6.9% (0.77 million dollars), and FVIII with 4.8% (0.54 million dollars) (70). The highest profit in the plasma industry is for IVIg which could be due to its vast clinical application. Besides, the low value of FVIII in the plasma industry of Iran could be due to the lower yield of this factor in the fractionation process.

Table. 2 **The supply and demand for PDMPs and the percentage of short-**

Product	Yield (per 1 L plasma)	Supply (according to the contract fractionation)	Price	Demand	Shortage (%)
Albumin	24.5 g	3400 kg	1.9 €/g	8500 kg	60
FVIII	160 IU	18 MIU	0.2 €/IU	120 MIU	85
FIX	200 IU	15 MIU	0.21 €/IU	15 MIU	0 (Surplus)
IVIg	4.5 g	700 kg	29.5 €/g	700 kg	0 (Surplus)

MIU: Million IU.

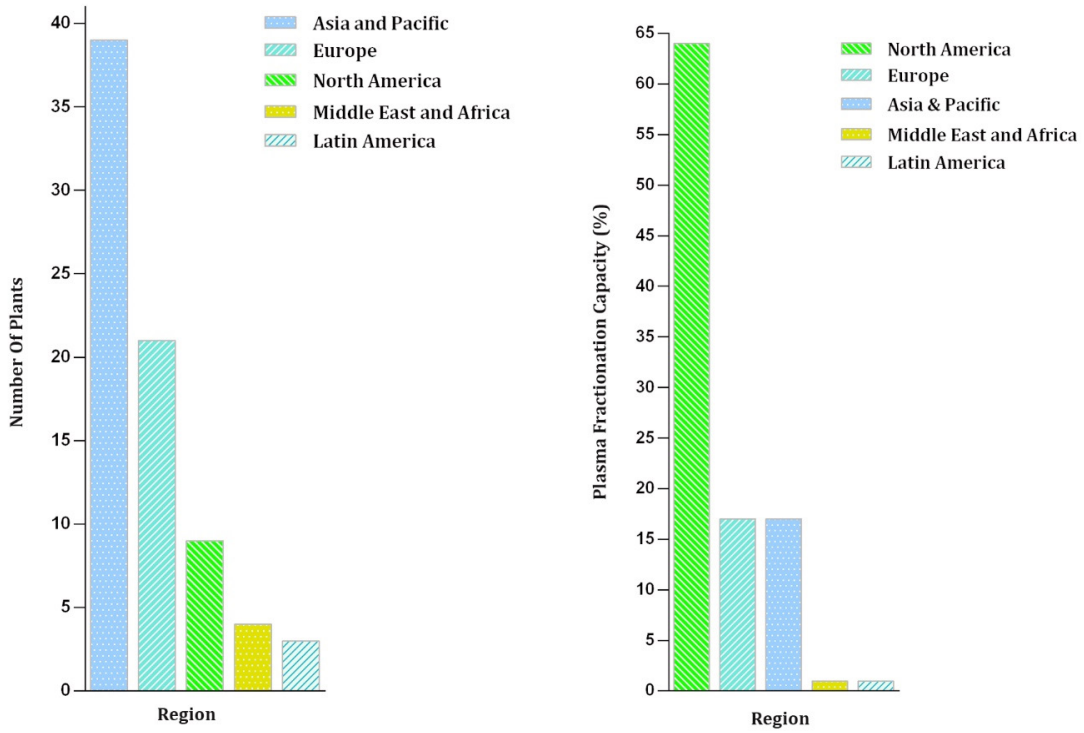

Figure 6. Plasma fractionation by regions. A) Asia and Pacific possess higher numbers of plasma fractionation plants than other continents (39 for Asia and Pacific, 21 for Europe, 9 for North America, 4 for Middle East and Africa, and 3 for Latin America) (source: Statista). B) The chief proportion of global plasma fractionation is related to North America (64%) and after that Asia and Pacific (17%), Europe (17%), Middle East and Africa (1%), and Latin America (1%) (data back to 2015) implying the great capacity of plants in North America, particularly in the U.S. (source: Marketing Research Bureau, Inc.).

supplied by 400,000 liters of collected plasma per year. Accordingly, Iran needs 1 million liters of plasma per year to meet the demands of the national health system for PDMPs (Fig. 8). This imbalanced supply and demand originated from some issues such as low number of centers for plasma supplement. As mentioned, the primary objective of IBTO is not to stimulate the blood donation just in order to elevate the production of plasma. The principle of IBTO was based on providing VNRBD; the goal which was achieved in 2007 with 100% rate of VNRBD (69). However, the private plasmapheresis centers could operate as a win-win plasma collection system in order to encourage more individuals to the plasma donation. Moreover, low recruited individuals to the plasmapheresis centers, low numbers of plasma-related companies which are parts of the contract fractionation program, and last but not the least, the limited investment in manufacturing domestic plasma fractionation are other challenges which should be considered in the future policy making in the scope of the plasma industry improvement in Iran (72). As stated, one of Iran's plans was to establish fractionation plants to respond the demands of the market. Initially, the construction of first plasma fractionator plant was finished in 1994. Under the

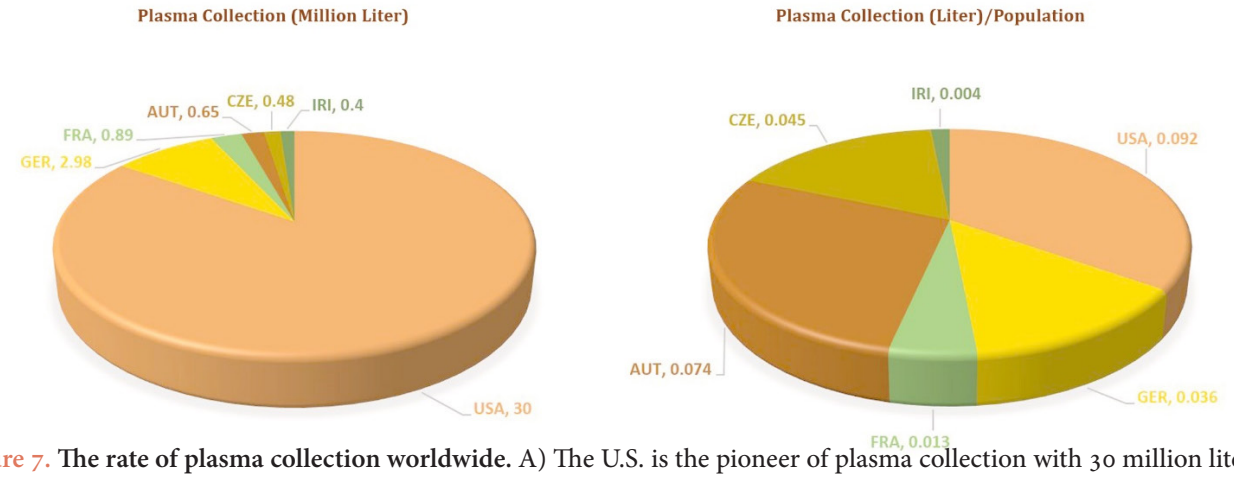

Figure 7. The rate of plasma collection worldwide. A) The U.S. is the pioneer of plasma collection with 30 million liters of collected plasma annually (2017). The difference between the U.S. and Germany with 2.98 million liters of collected plasma (2017) in the second rank is considerable. The amount of collected plasma in a year for Iran (2022) is near (still lower than) the Czech Republic (2017) and lower than Austria (2017) and France (2019) (source: Canadian Agency for Drugs and Technologies in Health [CADTH]). B) Interestingly, the ratio of plasma amount to the relevant date population shows that after the U.S. (0.092 liters of collected plasma per person) Austria with 0.074 L/person is in the second rank followed by the Czech Republic (0.045 L/person), Germany (0.036 L/person), France (0.013 L/person), and Iran (0.004 L/person). It could be concluded that Iran needs to deeply invest in plasma collection systems by establishing enough plasmapheresis centers and encouraging more and more people to donate plasma.

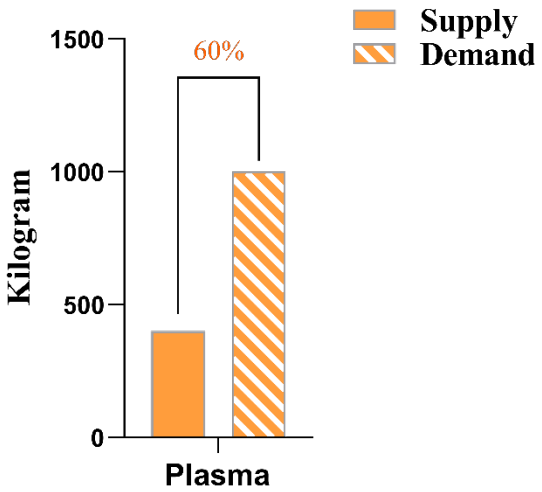

Figure 8. Plasma supply and demand in Iran. Annually, nearly 500,000 liters of plasma are collected through the collection systems in Iran (both recovered and source). However, Iran still needs more than 1 million liters of plasma to be collected per year to meet the demands of providing PDMPs in different situations of the health system.

supervision of IBTO, the primary capacity of the plant was 40,000 liters annually which was able to produce PDMPs such as albumin, coagulation factor, and Ig (like anti-rabies). In 1999, IBRF started to fractionate 80,000 liters plasma in order to produce PDMPs, however, due to diplomatic tensions and sanctions, the high-tech virus inactivation methods were not available. These political issues considerably hampered the process of establishing proper virus inactivation methods and actually this project was postponed for more than two decades. Despite much struggle with importation of infrastructures and the science of plasma fractionation in its primary states or even virus-removal methods, the construction of large-scale plasma fractionation plant has not happened yet, however, the small-scale fractionation of plasma with 50,000 liters capacity with the aim of producing albumin and IVIg was initiated and is ongoing now.

7. Conclusion and future prospects

The plasma industry began its initial steps in World War II. The efforts of Dr. Cohn's team ultimately lead to a primary method for the fractionation of plasma and currently reaches a modern technique yielding several elements called PDMPs. Regarding the clinical indications of plasma products in surgeries, liver and kidney dysfunction, numerous immunological and hematological disorders, hemophilia and thrombotic disorders, inflammatory conditions in infections and rheumatoid diseases, and so on, this industry achieved a high economic value in the world market.

Nowadays, several fractionation companies are working on the collected plasma from around the world to fractionate them into high-grade GMP PDMPs. In Iran, the first attempts in the plasma industry were started at the beginning of the IBTO establishment. However, Iran didn't have an infrastructure for plasma fractionation as well as for infection-removal strategies. Economical burdens and elevated demands for PDMPs propelled Iran to implement contract fractionation programs with high-tech companies whose products had been evaluated and approved by the policy of the Ministry of Health. On the other hand, currently more than 400,000 liters (both recovered and source) of plasma are obtained annually that are still lower to cover the demands of Iran that is approximately 1 million liters.

Putting the facts together that: i) the final costs of supplying PDMPs from exported plasma are lower than commercial sources; ii) Iran still has an unbalanced supply and demand for some PDMPs such as IVIg); and iii) the establishment of a domestic plasma fractionation plant is somewhat surplus of Iran's income indicates that the plasma industry in Iran needs more than ever attention. Regarding the experience of Iran in the plasma industry and possession of well-organized centralized transfusion systems, it is inferred that supplying PDMPs to patients in Iran could be provided if there will be additional efforts in the plasma industry. Nevertheless, establishing domestic plasma fractionation organizations which is a resource-intensive practice has been in the plans of Iran's health policymakers; but achieving this goal requires vast financial resources and applying the latest GMP standards. Taken together, it seems that increasing centers for plasma collection further than IBTO and encouraging people to recruit them to the plasma donation centers possibly by a win-win plasma collecting system could be a possible beneficial solution for policymakers.

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Conflicts of interest

The authors declare that they have no conflict of interest.

Data availability statement

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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