SUPPLY PROJECT

"Strengthening voluntary non-remunerated plasma collection capacity in Europe"

REPORT ON THE RESULTS OF THE: WP3 Task 3.3

Deliverable 3.6

"QUALITY OF COLLECTED PLASMA"

Evaluation of IgG monitoring in plasma manufacturing processes and data on IgG levels

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CONTENT

INTRODUCTION

Europe is facing an ongoing shortage of human plasma, which is essential for the production of life-saving medicines, and plays a vital role in various medical treatments[i]. The shortage has raised concerns among healthcare professionals, patients, and policymakers, highlighting the need to address this crisis[ii].

An aging populations, low awareness about plasma donation, and logistical challenges are influencing the availability of plasma. Additionally, the SARS-CoV-2 pandemic and associated restrictions have further limited donation potential. Simultaneously, the demand for plasma-derived medicinal products (PDMPs) is steadily rising. These products not only continue to be crucial for patients with immune deficiencies but also play an emerging role in new treatments of serious medical conditions[iii]. Without an adequate supply, those patients face the risk of inadequate treatment or unavailability of essential therapies, thereby compromising their health and quality of life. The shortage also places a financial burden on healthcare systems as they seek alternative treatments and import plasma or PDMPs from other regions. These are often more expensive, leading to increased healthcare costs for both patients and governments[iv].

Plasma quality criteria represent essential guidelines and standards set to ensure the safety, efficacy, and consistency of plasma and PDMPs. These criteria serve as a benchmark for plasma collection, processing, and testing, helping to safeguard the health of both donors and recipients. Donors must meet specific eligibility requirements, including age, overall health, and absence of infectious diseases that can be transmitted through plasma. Comprehensive screening protocols, including medical history assessments and laboratory tests, are implemented to identify potential risks and protect the safety of both donors and recipients. Europe-wide standards are delineated in the Pharmacopoeia and complemented by national guidelines. Collection methods, such as plasmapheresis or whole blood donation followed by plasma separation, represent standardized procedures to minimize the risk of contamination or improper handling. Thorough testing of donated plasma is crucial to identify potential infectious agents, ensure the absence of pathogens, and evaluate the quality and purity of the plasma. Testing methodologies in the European Union meet established standards and are performed by certified laboratories[v]. To further enhance plasma safety, pathogen inactivation and removal techniques are employed during the manufacturing process of PDMPs. Detailed records and documentation are maintained throughout the collection and manufacturing process, allowing for complete traceability of each donation. This ensures that any potential issues can be addressed promptly and product recalls can be efficiently executed, if necessary[vi]. Plasma quality criteria are often established and enforced by regulatory bodies, such as

the European Medicines Agency (EMA) in Europe. The manufacturing of PDMPs includes further safety steps following established protocols[vii].

Plasma donations involve the removal of plasma, which contains a significant proportion of proteins and immunoglobulins circulating in the bloodstream. Thus, plasma donation can temporarily lower the donor's protein and immunoglobulin levels, while the exact impact on protein levels varies from person to person[viii]. However, the body of healthy individuals has a remarkable ability to restore protein and IgG levels: within a relatively short time, these level in the blood typically return to normal. To ensure donor safety and prevent any adverse effects, plasma donation centres monitor protein and immunoglobulin levels in potential donors[ix]. When it comes to plasma donations, the IgG yield—the amount of immunoglobulin G (IgG) obtained from a donor's plasma—plays a crucial role in meeting the demand for PDMPs.

According to the European Pharmacopoeia the total protein content of a unit of plasma for fractionation should be at least 50g/l but depends on the serum protein content of the donor. At the same time, Directive 2002/98/EC[1] and Directive 2004/33/EC[2] need to be respected regarding donor safety and quality of blood components, stating that the protein level in donor's blood needs to be above 60g/l.

Because of the current high demand for immunoglobulins (IgG) as PDMPs, collection strategies should focus more on a proper yield of qualitative IgG in donated plasma. We defined quality of plasma as content of total protein (TP) and IgG. The donor's initial IgG levels can have a significant impact on the overall IgG yield of the donation. Therefore, selecting donors with higher IgG levels can result in a higher overall IgG yield from their plasma donation. Plasma undergoes processing and fractionation to extract and purify specific components, such as IgG, for therapeutic use. Higher initial IgG levels in donated plasma can enhance the recovery of IgG of this process. To maximize the IgG yield of plasma donations, careful donor selection and management of donation frequencies seems most important.

To establish recommendations on how to efficiently collect plasma with a high yield of these plasma proteins we evaluated information in a dedicated study to assess both donor characteristics and IgG and TP quality in plasma. Plasma values were analysed in correlation with donor characteristics and frequency of donations. We also discussed a dedicated cost model based on the integrated data with relevant stakeholders during a virtual workshop.

[1] Directive 2002/98/EC of the European Parliament and of the Council of 27 January 2003 setting standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components and amending Directive 2001/83/EC.

[2]Directive 2004/33/EC of 22 March 2004 implementing Directive 2002/98/EC as regards certain technical requirements for blood and blood components

KEY STATEMENTS OF PLASMA FRACTIONATORS

The following statements of leading plasma fractionators were obtained as a result of a virtual workshop and E-Mail conversations between October and November 2022. They represent informal exchanges, rather than official statements. The views of the interlocutors may have changed over time and were at no time regarded as legally binding.

- Fractionators demand the adherence to the national guidelines for haemotherapy regarding IgG/protein levels in donors and donation frequencies.
- All calculations and pricings of plasma donations are volume and not IgG/protein content based.
- IgG/protein values are not being individually measured as reception control but only in plasma pools. Therefore the required pool size depends on the fractionator's protocols.
- The IgG/protein testing at the level of manufacturing pools are part of the monitoring of manufacturing process in validated conditions. Details within the manufacturing process can be adjusted if indicated by those interim controls (for example if IgG levels are unexpectedly high/low).
- Internal observations show that the deviation of IgG/protein concentrations in plasma pools does normally not exceed +/- 5%.
- IgG/protein concentration has an impact on the yield during fractionation but not on the IgG-content and quality of the final PDMPs.
- A functionally relevant performance difference between PDMPs out of plasma with low or high IgG concentration or low or high donation frequencies was not reported.
- Recovered plasma is not actively used to compensate lower concentrations in source plasma pools.
- The fractionators regard IgG/quality based pricing as an interesting option, but there are currently no plans to implement such a system.
- For solving plasma shortage and increase plasma volumes collected in Europe, fractionators consider the approval of commercial and remunerated plasma donations in more European countries as the most relevant action.

PROSPECTIVE APPROACH DERIVED FROM THE KEY STATEMENTS OF STAKEHOLDERS

While pricing based on the IgG level of the individual donation is not economically favourable, quality based pricing might be implemented based on IgG content of a larger pool/delivery. The production process may be adjusted accordingly, based on measured IgG content. This might allow to predict more precisely the necessary volume of collected plasma to obtain the targeted amount of IgG. However, there are currently no plans yet to implement such a system.

RESULTS OF DATA ANALYSIS ON IGG LEVELS IN PLASMA DONORS

For the analysis of IgG levels in plasma donors, data was extracted from the internal database which includes data on plasma donations in the Red Cross Blood Service Baden-Württemberg - Hessen and North-East (DRK-BSD BaWüHe and NE).

THE DATASET

The dataset was extracted from the medical database used in the DRK-BSD BaWüHe and NE. Data included all measurements of IgG levels in the area covered by the DRK-BSD BaWüHe and NE in 2021 and 2022 (figure 1 B). Data extracted from the database included serological values, anamnestic information and donation history in the time interval of 1 to 24 months before the measurement (figure 1 A). According to the German Guidelines, IgG level in the donor has to be measured at the first plasma donation and every 5th donation thereafter.

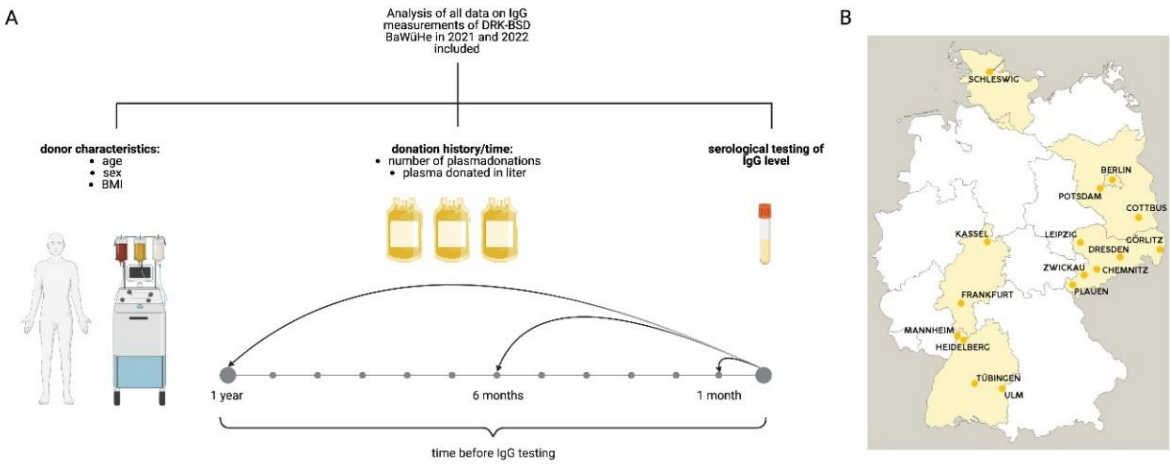

FIGURE 1
The figure shows the data included in the analysis and the regions of Germany covered by the analysis.

The dataset included 80,733 measurements in total. Blood samples were taken from each donor directly before plasmapheresis. The results were available one or two days later. The same IgG serological test method was used throughout the whole study. As the dataset had some missing values especially in the section of serological data, the total number of values of some parameters

may differ. The values refer to 23,808 donors. If the IgG-level of a plasma donor was measured below a certain threshold, the donor was deferred to allow recovery. Donors were only allowed to continue plasma donation when IgG levels returned to normal (above 6.0 g/l). If the IgG value was still too low, the donor was deferred again. After three measurements below threshold, the donor was deferred permanently from plasma donation. However, it was not the purpose of this investigation to collect data on donor deferral and readmission. In the following section we focus merely on plasma content of the donations which we were able to collect following the above mentioned selection strategy.

In this section, we discuss all measured values potentially including repeated measurements of the same individual within the two years of the observation phase. The population had a median age of 40 years. 42.94% of measurements referred to female donors (figure 2 A). In the last month donors donated between 0 up to 9 times (median: 1), up to 49 times within the last 6 months (median: 7), up to 60 times within the last 12 months (median: 11) and up to 121 times within the last 24 months (median: 17). Those numbers of donations lead to volumes of up to 9.98 liters (median: 1.2 liters) within the last month, 41.36 litres (median: 5.6 liters) the last 6 months, 58.6 litres (median: 9.6 liters) the last 12 months and 111.3 litres (median: 15.0 liters) the last 24 months. Those volumes do also include plasma donated in connection with a donation of whole blood or platelets (figure 2 B).

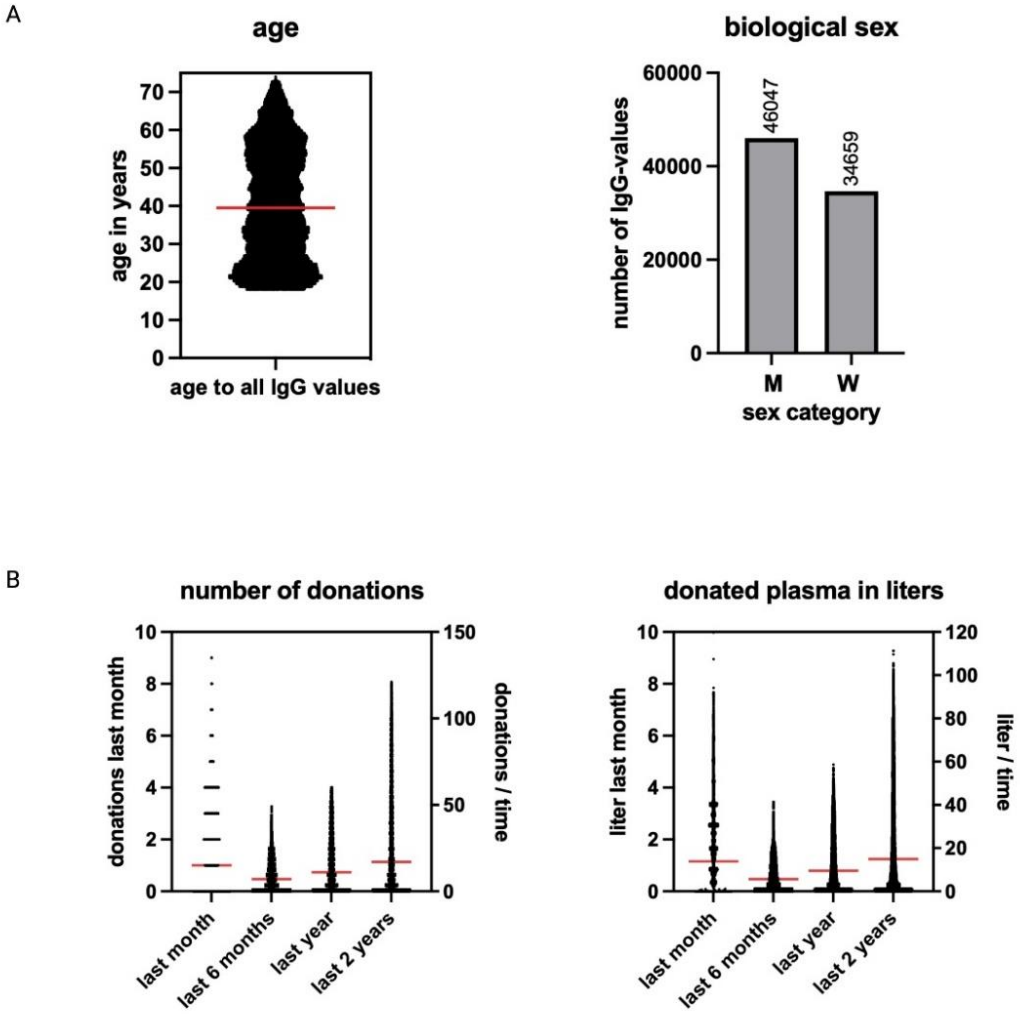

FIGURE 2
Age, biological sex and donation history of all 80,733 IgG measurements (from 23,808 donors) in DRK-BSD BaWüHE in 2021 and 2022. A) The median of age was 39.5 years and 42.9% of the donors were female. B) Overview of donation history within the dataset. Individuals donated up to nine times and up to 9 litre within the last 30 days.

FACTORS INFLUENCING IGG AND PROTEIN LEVELS

An assessment of influencing factors on IgG levels was conducted. The number of donations within defined timeframes turned out to be single the most relevant parameter (figure 3). The impact of weight, BMI (Body Mass Index), and sex on IgG levels, in the context of plasma donation, can vary among individuals. Some studies suggested that individuals with higher weight or BMI may have higher IgG levels. This may be attributed to increased overall blood volume and potentially higher plasma protein concentrations in individuals with larger body size. However, the relationship

between weight/BMI and IgG levels was not consistent across all studies, and individual variations may occur. We could not confirm a significant correlation between weight/BMI and protein/IgG in our dataset of all 80,733 IgG measurements. Some studies indicated that sex tends to make a difference in IgG levels potentially being influenced by hormonal factors. However, the variations in IgG levels between sexes are generally small and should be considered within the context of overall individual differences. It's important to highlight that the impact of weight, BMI, and sex on IgG levels is not universally consistent among all individuals, and the relationship can be influenced by multiple factors. IgG levels are influenced by a complex interplay of genetic, physiological, and environmental factors that can differ considerably from person to person.

We analysed the IgG level and correlated it with the number of donations within the month before the measurement. The results identified a significant decline of IgG levels when comparing controls (no donation within the last 6 months), donors with no donation within the last month, low frequency donors (1-2 donations last month), medium frequency donors (3-4 donations last month) and high frequency donors (>4 donations last months) (figure 3).

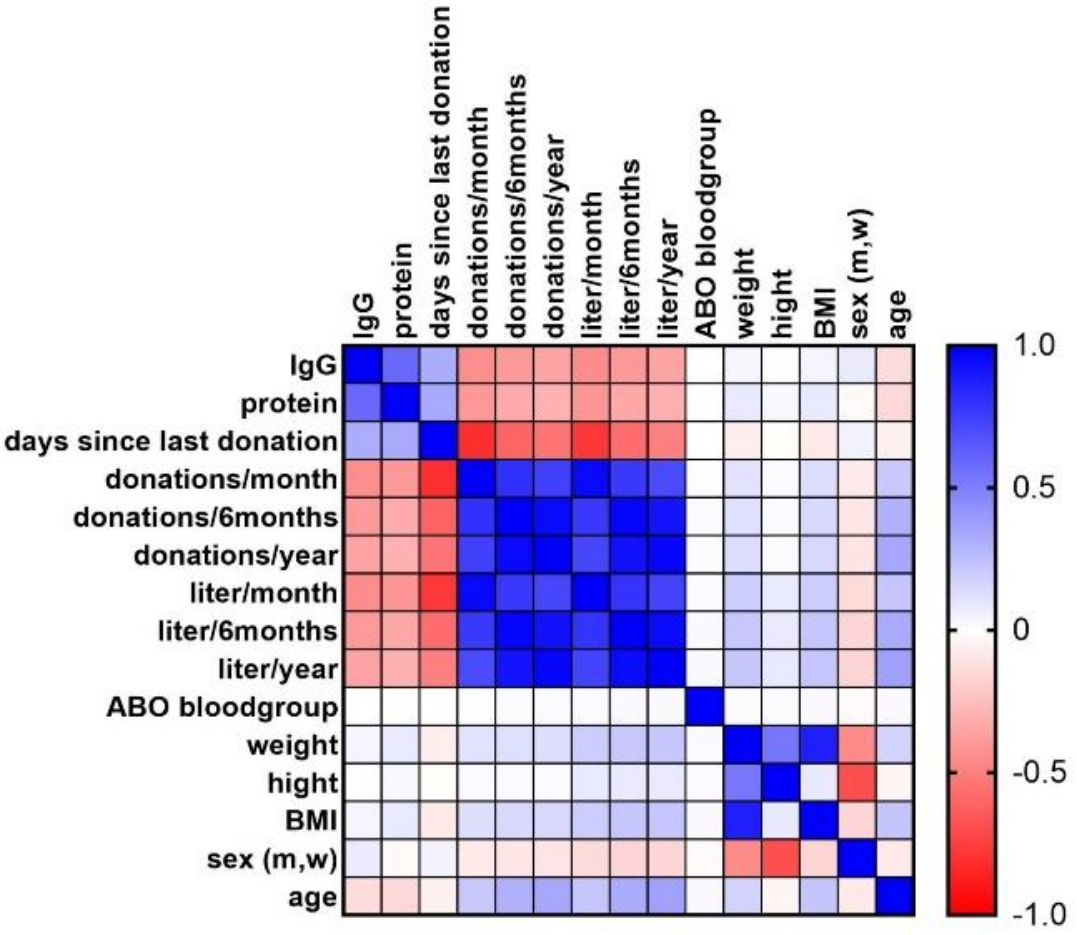

FIGURE 3
The heatmap shows the pearson correlation between investigated parameters in either blue (positive) or red (negative).

Additionally, the correlation analysis of IgG-levels and number of plasma donations such as donated plasma in litres showed correlations with R squared of 0.17 (figure 34).

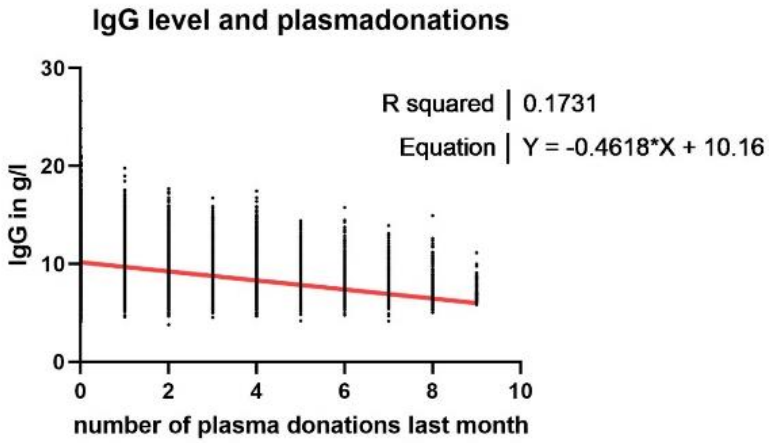

FIGURE 4
The graphs show the influence of donations within the last month on IgG levels.

It is important to differentiate between naturally occurring variations in IgG levels among individuals and the specific impact of plasma donation on IgG levels. To further analyse influencing factors on resilience to IgG-harvesting in donors, we looked at characteristics of subgroups of high frequency donors (5-9 donations within the last month). The group of high frequency donors was divided into four subgroups according their IgG level (<6 g/l; 6-7.9 g/l; 8-9.9 g/l; >10 g/l). The mean in age, BMI and weight of donors in the >10 g/l group was higher than of the other groups. Age, BMI and weight were identified as slightly protecting factors from IgG-loss in high frequency plasma donors (figures 5, 6 and 7).

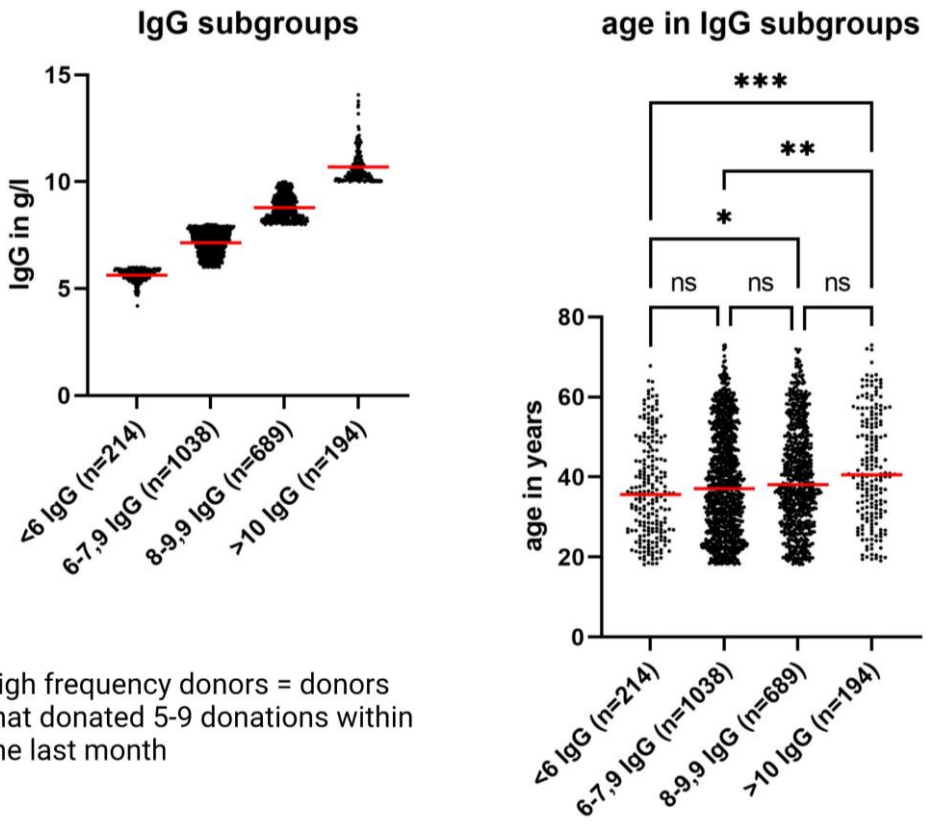

FIGURE 5
Characteristics of IgG-levels and age of the different high frequency donor subgroups.

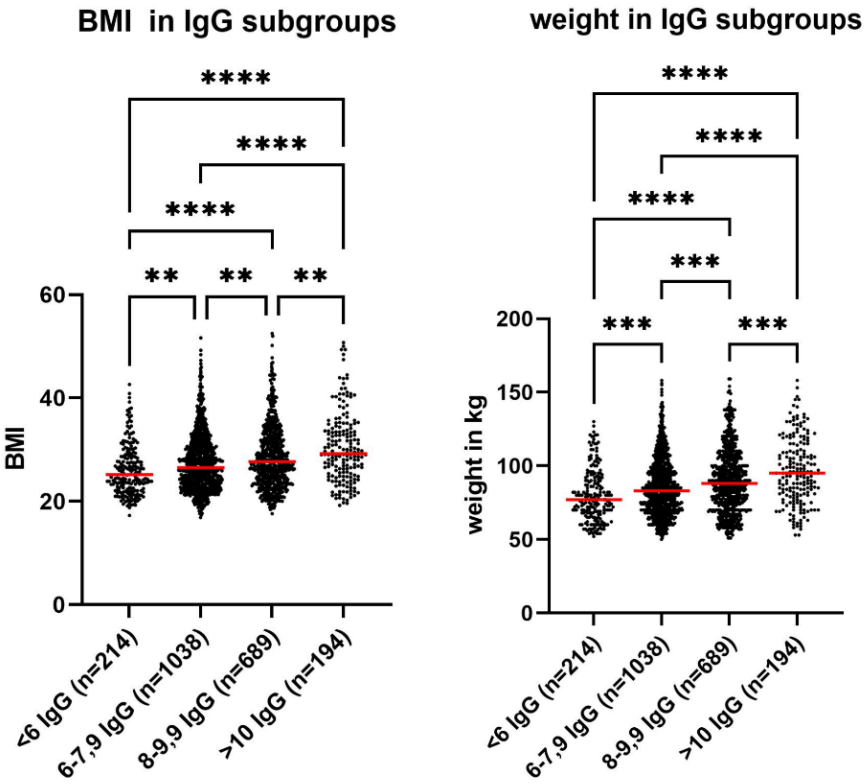

FIGURE 6

Characteristics of BMI and weight of the different high frequency donor subgroups and correlation between weight/BMI and IgG-levels in the group of donors, which donated 5-9 times within the last month. However, donors with underweight (below 50 kg) or excessive obesity were deferred. This may potentially represent a confounder.

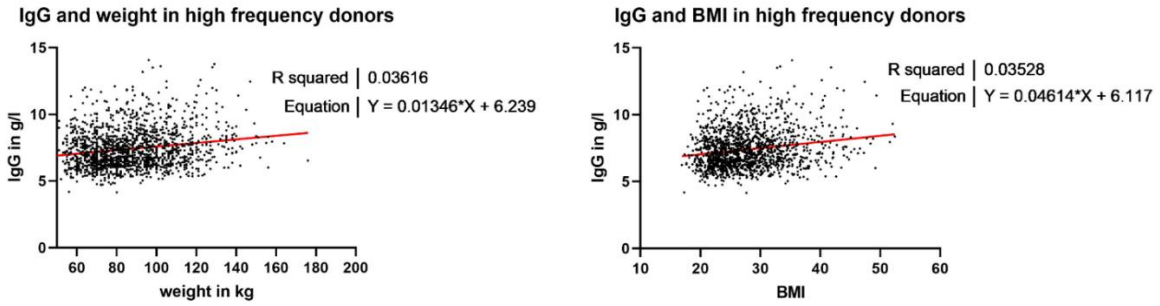

FIGURE 7

Correlation between weight/BMI and IgG-levels in the group of donors, which donated 5-9 times within the last month.

DEVISING VARIOUS CASE SCENARIOS

As European countries have different guidelines for donation frequency, this will most likely result in plasma with different IgG content. Additionally, local policies on donor management can result in further differences even between individual plasma centres.

A hypothetical case scenario based on a delivery of 2,000 litres from a donation centre with regulations in place allowing only one donation every two weeks would result in a higher total amount of IgG than from a centre where plasma donation is possible every 3 days. We designed a fictional scenario for those two centres grouping all measurements of donors (i.e. at least one donation within the last 6 months) with max. two donations within the last 30 days (category 1) on the one hand and all measurements of donors with 3 to 9 donations within the last 30 days (category 2) on the other one. While this hypothetical scenario is not based on real donations centres, it may allow calculating the impact of donation frequency policies on the resulting deliveries. To obtain the IgG content per delivery, we multiplied the median IgG value with an average pool volume of 2,000 litres. The numbers of the two hypothetical centres were compared with a third hypothetical centre that only collects plasma from “controls” (individuals that did not donate plasma within the last 6 months). In this case scenario the resulting pools between the two centres showed a considerable difference of IgG of over 2,000 g, which is 10% of the total amount (figure 8).

In terms of total IgG donated per month, high frequency donors obviously donate significantly more than individuals with low donation frequency. This has to be considered when discussing solutions for absolute plasma shortage. Although IgG-levels are slightly lower in high frequency donors, it is important to motivate them to continue to donate, provided that all eligibility criteria are met.

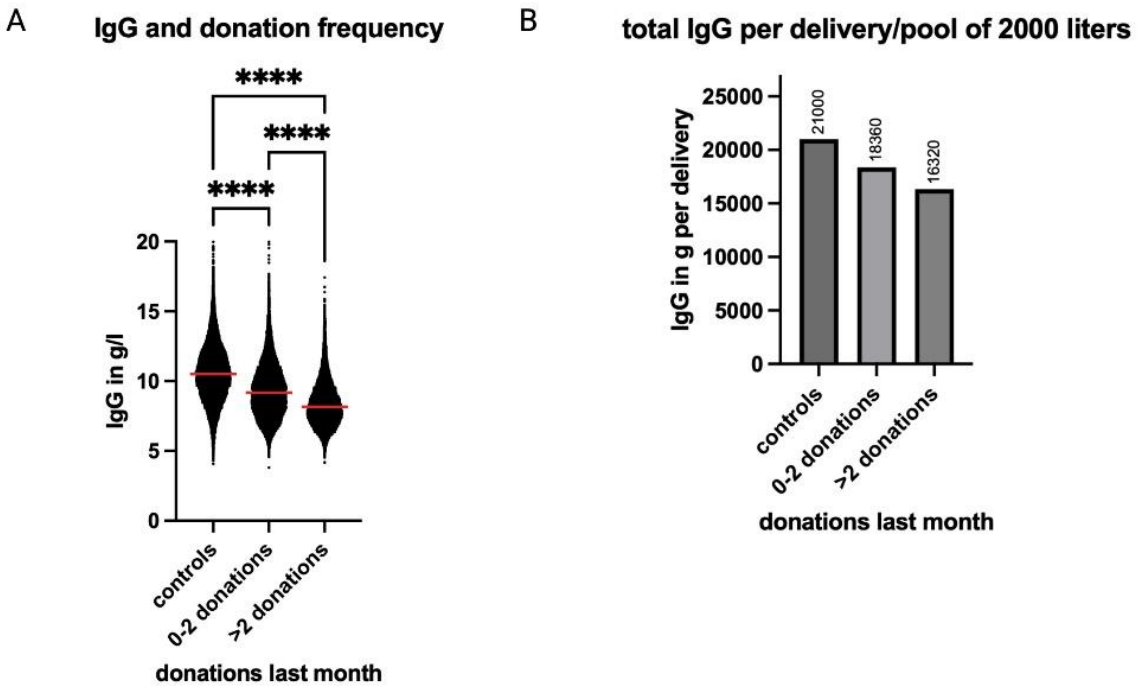

FIGURE 8
A fictional scenario with two groups of donors was analysed: category 1 donors* with max. 2 donations within the last 30 days on the one hand, and category 2 donors with >2 donations on the other.
A) Shows the IgG levels measured in the two categories compared to "controls"**.
B) Shows the resulting IgG content in a 2,000 litre pool.

*Category 1 donors = at least 1 donation within the last 6 months and max. 2 donations within the last 30 days.
** Controls = no donation within the last 6 months.

Based on the results of our investigation we suggest that fractionators may test IgG content of plasma pools during the fractionation process with a correlation to the plasma starting pool origin and plasma origin and type. A pricing model based on the IgG-content would thus be an obvious option by compensating the delivering donation centre according to the calculated IgG amount based on a market price for "raw IgG".

To further address the question on the optimal donation frequency to overcome plasma shortage, it is appropriate to calculate which absolute IgG amount per month was donated from a donor that donated 1-9 times per month. To investigate the expected amount of donated IgG per month, we multiplied the IgG level measured with the plasma volume donated within the last month (figure A). Thus, the calculation was based on real world data, also including data on early donation terminations due to unexpected donation events. As most European countries allow max. one donation every two weeks, we calculated values for 3 groups: "low frequency" (=1-2 donations per

month), “medium frequency” (= 3-4 donations per month) and “high frequency” (>4 donations per month) of donation. Using this model, a low frequency donor would donate 10 g of IgG per month (median), a medium frequency donor 22 g of IgG per month (median) and a high frequency donor 35 g of IgG per month (median, figure B).

We further plotted the values of donation frequency and donated IgG within the last month in an x/y-graph. As expected, this led to a flattening curve over time (purple) and laying below a line of hypothetical steady IgG levels of 9 g/l in a donor donating 750ml per donation (black) (figure B).

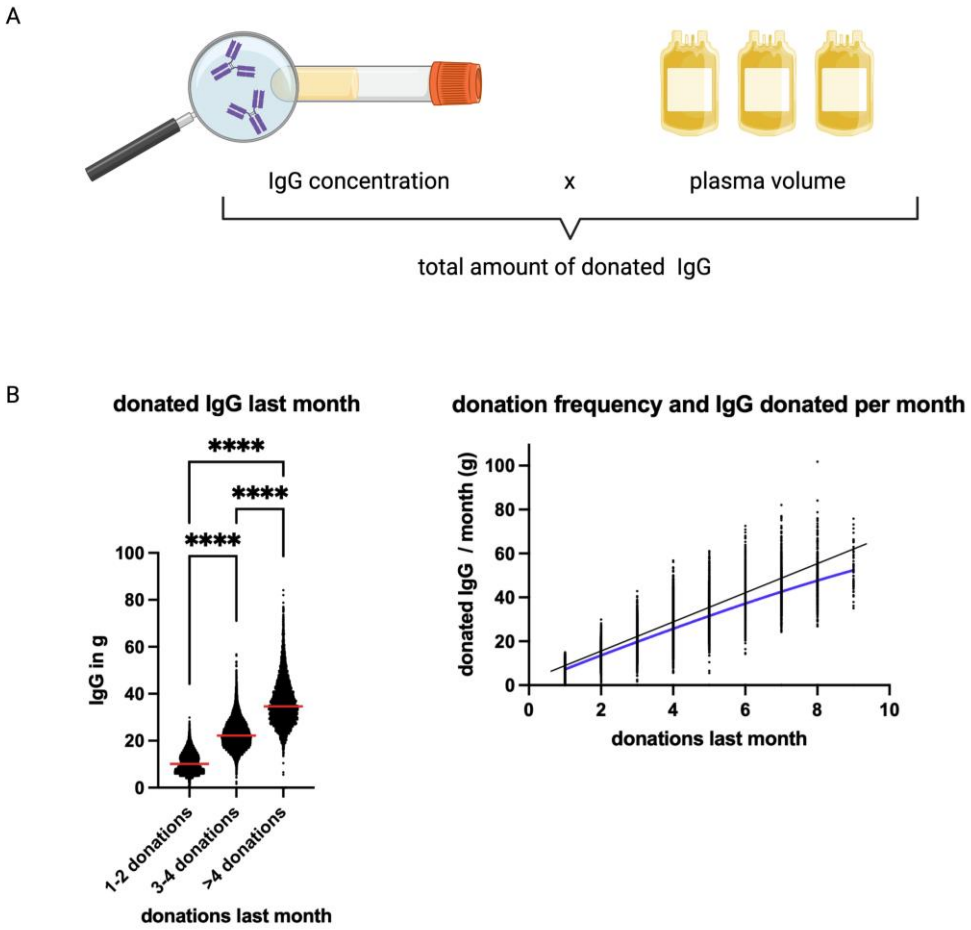

FIGURE 9

A) Measured IgG level, multiplied with the donated plasma volume within the last month, resulting in the total amount of IgG donated within one month.
B) Shows the total amount of IgG donated within one month depending on donation frequency and IgG levels. Using this model a low frequency donor* would donate 10g of IgG per month (median), a medium frequency donor** 22g of IgG per month (median) and a high frequency donor*** 35g of IgG per month. Plotted values of donation frequency and donated IgG within the last month in an x/y-graph resulted in a curve flattening over time (blue) and laying below a line mimicking an IgG amount with steady IgG levels of 9 g/l in a donor donating 750ml per donation (black).
*low frequency donors = 1-2 donations last month
**medium frequency donors = 3-4 donations last month
***high frequency donors = >4 donations last month

CONCLUSIONS AND OUTLOOK

- IgG concentration in donors has a considerable impact on the IgG recovery yield during subsequent fractionation.
- Different regulations on donation frequency influence the yield of IgG in donations.
- IgG content in pools with different background in donation frequency could differ over 10% making IgG based compensation worth a discussion.
- IgG/protein values are being measured at pool levels depending on the fractionators protocols (for example 1,000 to 3,000L equals one “delivery”) and would allow a calculation of IgG per delivery in gram.

The plasma shortage in Europe poses a significant challenge to healthcare systems, patients, and advanced therapeutical strategies. Addressing this crisis requires a comprehensive approach involving increased awareness, effective donor recruitment strategies, international collaboration, and continued research and innovation. It also include the investigation and optimization of quality criteria such as protein and IgG levels. While even long-term plasma donation is safe[x], it has an impact on protein and immunoglobulin levels in the donor's blood. Those levels have a significant influence on the IgG yield obtained from plasma donations. Selecting donors with higher initial IgG levels may help to maximize the overall IgG concentration in donated plasma, thereby contributing to a more abundant supply of PDMPs. An IgG based pricing model may put emphasis on this crucial parameter.

DISCLOSURES

Statistics and visuals have been created with Prism Graphpad and BioRender.

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